



VOLUME XV

1936

# MEDICINE

*Analytical Reviews*  
of  
General Medicine  
Neurology and Pediatrics

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THE WILLIAMS & WILKINS COMPANY  
BALTIMORE, MD

1936



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# ARTIFICIAL PNEUMOTHORAX IN LOBAR PNEUMONIA<sup>1</sup>

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## INTRODUCTION

Artificial pneumothorax appears to have been first used in the treatment of pneumonia during the influenzal pandemic of 1918-19 by Adolphus D Rood (1), first Lieutenant, Medical Corps, U S Army, at Takoma Park, D C In a paper entitled "A Clinical Study of Influenza Pneumonia," published in the New York Medical Journal in its issue of March 22, 1919, page 499, he writes in connection with a discussion of diagnostic lung puncture, as follows

"It was interesting to note that often the patient was greatly relieved by lung puncture, especially if a pneumothorax followed the operation, and it was not uncommon for patients to request that the operation be repeated. Patients frequently showed a drop in temperature following puncture and

<sup>1</sup> Presented in part before the Harvey Society, April 18, 1935 Aided by a grant from the Research Fund of Yale University School of Medicine and by gifts from Mr Howard L Goodhart and Mr Robert W Huntington

a temporary improvement in physical signs The cough and sputum would increase for a short time, followed by a marked decrease in the number of râles within a few hours

"The results following this procedure led to the opinion that the production of a slight positive pressure in the side showing greater involvement might materially aid in compressing the profuse exudate from the affected lobes With this purpose in view, an artificial pneumothorax was produced in three patients, injecting from 100 cc to 150 cc of air into the pleural cavity, in the same manner as has been frequently carried out in the treatment of tuberculosis

"These three cases were considered hopeless at time of injection Two of the patients recovered, but the third one died three days following operation Special mention of this case is of interest At the time of pneumothorax the patient had been very ill for four days and was considered hopeless, being intensely cyanosed, delirious, and moribund beyond a doubt One hundred cubic centimeters of air were injected into the left pleural sac The following day the patient became conscious and rational, and very few râles were to be heard in the chest of the side operated upon and breath sounds were quite distinct He continued to improve for thirty-six hours, when he again became delirious and comatose, dying forty-eight hours after operation

"Autopsy showed a pneumothorax still present The lower lobe was compressed to one-third its normal size and did not contain the usual amount of exudate, while the upper lobe which was not hemorrhagic showed but little compression and its functions were not interfered with by the artificial pneumothorax The use of this operation as a therapeutic measure in selected cases is worthy of further trial "

At about the same time and quite independently Friedemann (2) of the Rudolph Virchow-Krankenhaus in Berlin, undertook the use of artificial pneumothorax in the treatment of patients with lobar pneumonia and in 1921 recorded the results obtained in seven cases Familiar with the favorable effects of artificial pneumothorax in pulmonary tuberculosis, it occurred to him that its application in pneumonia might exert a beneficial influence on the course of the disease, in part by separation of the pleural surfaces but especially by immobilization of the acutely inflamed and constantly moving lung This supposition was apparently borne out, for he reports that during the introduction of air pleural pain diminished, breathing became easier, and the appearance of anxiety lessened Subsequently the

general toxic appearance diminished and the fever subsided, usually by lysis, though in one early case treated on the second day, recovery occurred on the third day by crisis

Meanwhile W H Wynn (3), Hon Physician to the General Hospital, Birmingham, had been employing artificial pneumothorax in the treatment of pneumonia, for he writes in the September 2nd issue of the Lancet, 1922, page 496, as follows "In a few cases with very severe pain I have separated the pleural surfaces by the introduction of a small quantity of oxygen This is not difficult to those accustomed to artificial pneumothorax treatment, and I was favorably impressed with the immediate relief given " And again in the Birmingham Medical Review (4),—"I have used this method in a few cases of *acute pneumonia* in which the pain has been very severe The change in a patient who is sleepless, restless, groaning, and exhausting himself to a condition of comparative ease is remarkable He often goes to sleep and the temperature falls The absorption of 300 or 400 cc of oxygen from the pleura must also be of some value " No further details are recorded

These initial reports appear to have stimulated little interest, for during the ensuing ten years only three papers on the use of artificial pneumothorax in acute pneumonia appeared,—the first in 1921 by David (5), who reported very briefly on the treatment of six cases, the second in 1928 by Schottky (6), who reported on the treatment of one case, and the third in 1931 by Taylor (7), who reported on three cases treated with oxygen primarily for the relief of pleural pain as advocated by Wynn (3)

Although no other communications on the use of artificial pneumothorax in acute lobar pneumonia appeared during this period of ten years, four papers were published dealing with the use of artificial pneumothorax in the treatment of prolonged and complicated cases of bronchopneumonia in infants and young children In 1928 Ibrahim and Duken (8), having observed the critical recovery of an infant 10 months of age immediately following a traumatic pneumothorax brought on by thoracentesis for an interlobar pleural effusion, reported the use of artificial pneumothorax in two infants with bronchopneumonia, in one case complicated by an interlobar pleural effusion, in the other by bronchitis and probable bronchiectasis Apparently

favorable results attributed by them to the treatment ensued. In 1929 Klotz (9) described the treatment of four similar cases in children with critical cure in one, apparent benefit in a second, questionable effect in a third, and no effect in the fourth. In 1930 Duken (10) reported five additional cases and Jahr and Neumann (11) added five more in the same year. The use of artificial pneumothorax in prolonged and complicated cases of bronchopneumonia in infants and children obviously has little bearing on the use of this procedure in acute lobar pneumonia and consequently need not be discussed further here.

In 1932, following Coghlan's (12) stimulating report on the treatment of six cases of acute lobar pneumonia, a widespread study of the usefulness of artificial pneumothorax in this disease began. Thus, in the same year, Perlroth and Topercer (13) reported on the treatment of 7 cases, Guadarrama (14), 1 case, Viswanathan (15), 7 cases, Anderson (16), 3 cases, and Li (17), 6 cases. In 1934 Moorman (18, 19) recorded 10 cases, Lieberman and Leopold (20), following a study of the effect of artificial pneumothorax on experimental lobar pneumonia in dogs, 1 case, Behrend and Cowper (21), 11 cases, Blake, Howard and Hull (22), 22 cases, and in 1935 Hines and Bennett (23), 12 cases, and Holmes and Randolph (24), 18 cases, making a total of 124 cases.

All of these reports have dealt largely with the effect of artificial pneumothorax on the clinical phenomena and course of pneumonia. In addition some have engaged in a purely theoretical discussion of the mechanisms by which the observed effects were supposedly brought about. With commendable caution nearly all have avoided a statistical analysis of the effect of artificial pneumothorax on the case fatality rate, the incidence of complications and the duration of the disease and there would appear to be no valid reason for undertaking such an analysis at present, since the material dealt with is highly selective and the variables are too numerous and immeasurable to justify mathematical treatment.

Four matters of interest, however, may be briefly commented on, namely, the apparent influence of artificial pneumothorax on at least some of the clinical phenomena of lobar pneumonia, its apparently variable effect on the course of the disease, the procedure followed with respect to the frequency of treatments and the amount of air intro-

duced, and the theoretical reasons which have been advanced in explanation of the beneficial influence which artificial pneumothorax is supposed to exert

The four most striking clinical effects recorded are (a) prompt relief of pleural pain, an occurrence emphasized by nearly all who have used the method, (b) relief of dyspnea, a phenomenon particularly referred to by Friedemann (2), Taylor (7), Coghlan (12), Behrend and Cowper (21), Hines and Bennett (23), and Holmes and Randolph (24), (c) the frequent, though by no means uniform occurrence of a critical fall in temperature shortly after the induction of artificial pneumothorax, sometimes permanent, though often only temporary, a phenomenon stressed particularly by David (5), Coghlan (12), Perlroth and Topercer (13), Guadarrama (14), Anderson (16), and Behrend and Cowper (21), and (d) a marked improvement in the so called general toxic phenomena of the disease, emphasized especially by Friedemann (2), Coghlan (12), Moorman (19), Behrend and Cowper (21), and Holmes and Randolph (24) Other less frequently recorded clinical effects have been diminution of cyanosis, lessening of cough, and decrease in the amount of sputum (21), and in one case relief from persistent hiccoughs (23)

The possible effect on the course and outcome of the disease is extremely difficult, if not impossible, to evaluate from a critical study of the cases reported in the literature, in the first place because bacteriological studies of the type of infection are recorded in only a few instances (20, 21, 22, 24), the presence or absence of bacteremia even less frequently (20, 21, 22) and the time of appearance of humoral antibodies only once (22), and in the second place because a large majority of the cases have not been treated until the fourth day of the disease or later (fig 1)

Such analysis, however, as can be made from the data presented would seem to show that under treatment with artificial pneumothorax lobar pneumonia pursues one of three courses, making it possible to divide the cases into three groups (fig 1) In the first group comprising 46 of the 93 cases analyzed,<sup>2</sup> there was no noticeable effect on

<sup>2</sup> In this analysis 6 cases of bronchopneumonia, 3 cases in which the day of the disease was unknown, and the 22 cases reported by Blake, Howard and Hull (22), have been omitted



the course of the disease. Ten of these cases died. In the second group, comprising 22 of the 93 cases, temporary more or less marked improvement followed the use of artificial pneumothorax but relapse often occurred and the disease subsequently followed either its usual or a somewhat moderated and perhaps shortened course. In the third group, comprising 25 of the 93 cases, critical and permanent recovery followed within a period of twenty-four hours after the introduction of air into the pleural cavity. It is noteworthy, however, that of the 25 cases in this third group 21 were first treated on the fourth day of the disease or later and, consequently, the apparent cure

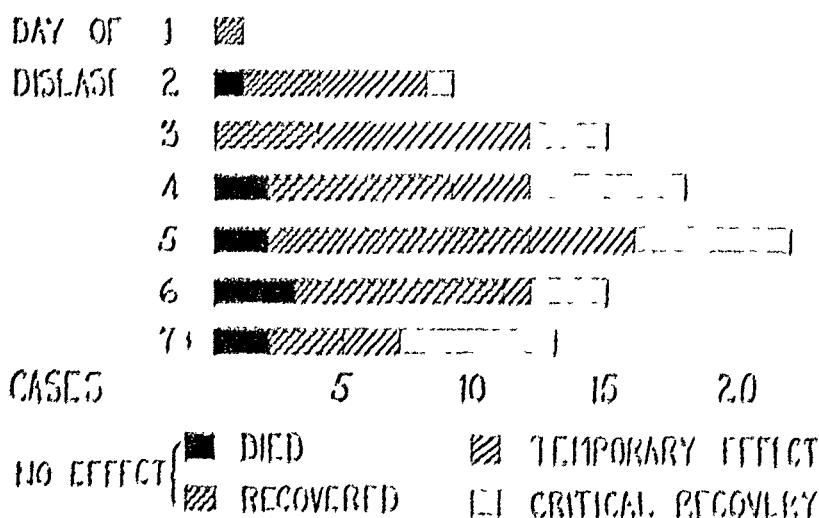


FIG. 1. EFFECT OF ARTIFICIAL PNEUMOTHORAX ON THE COURSE OF LOBAR PNEUMONIA IN 93 CASES REPORTED IN THE LITERATURE.

cannot with any assurance be attributed to the use of artificial pneumothorax but may have been and probably was in many instances, due to the natural termination of the disease. It is further noteworthy that only 1 of the 10 cases treated on the first or second day of the disease and only 3 of the 15 cases treated on the third day exhibited a critical recovery within twenty four hours after the institution of treatment.

In connection with the foregoing brief analysis it seems pertinent to point out here for reasons which will appear subsequently in the presentation of our own cases, that 34 of the 93 cases received only one treatment, that 46 cases received only two treatments, usually

administered from 18 to 48 hours apart, while only 11 cases received a third treatment and only 2 a fourth. It furthermore should be emphasized that the amount of air introduced into the pleural cavity at each treatment was usually not more than 300 to 500 cc and that only 9 cases received a total of more than 1000 cc, the maximum amount given being 1650 cc in 2 cases. From this data it would appear that insufficient air was introduced to cause more than a moderate collapse of the involved lung in the great majority of cases, particularly if the collapse was not selective, and there is no significant evidence presented to show that selective collapse of the involved lobe took place nor does a study of the roentgenograms portrayed (19, 21, 23, 24) indicate that such was the case.

Three major theories have been advanced in explanation of the influence of artificial pneumothorax on the clinical course of lobar pneumonia, adherence to a particular theory apparently having depended upon the author's conception of the pathogenesis and nature of the disease.

The most frequently advocated theory is that advanced by Friedemann (2), namely, that pneumothorax immobilizes or at least rests the acutely inflamed and constantly moving lung, thereby reducing the absorption of toxic products. He believes that this is accomplished by checking the drainage of lymph from the affected lobe. At the same time separation of the inflamed pleural surfaces assists by relieving pleural pain with consequent mental and physical rest, which are believed by Wynn (4), Taylor (7) and Viswanathan (15) to be of the greatest importance. The foregoing theory is in the main subscribed to by David (5), Schottky (6), Coghlan (12), Anderson (16), Moorman (19) and Behrend and Cowper (21), but with minor modifications or additions. Thus Schottky (6), Coghlan (12), Anderson (16), Moorman (19) and Holmes and Randolph (24) suggest that the diminished toxemia following artificial pneumothorax is due to diminished blood flow through the collapsed lung with consequent decrease in the amount of toxic products entering the general circulation, while David (5) believes that there is hyperemia of the collapsed lung which serves to promote healing. Coghlan (12) and Behrend and Cowper (21) further suggest that anoxemia is lessened, since a decreased amount of unoxygenated blood will enter the general circulation.

While most of those who believe that the blood-flow through the collapsed lung is diminished, attribute this directly to the presence of the pneumothorax, Duken (10) argues that the lower intrapleural pressure on the untreated side draws a larger proportion of blood to that lung. Friedemann's theory, which may properly be designated "the lung rest" theory, would appear to depend upon the conception that lobar pneumonia is primarily a bronchogenic, local, pulmonary infection, the general phenomena of which are due to the absorption of toxic products from the inflamed lung, either by lymphatic drainage or directly into the blood stream.

The second theory is that proposed by Perlroth and Topercer (13) and depends upon their stated belief that lobar pneumonia is primarily a general infection with secondary elective localization of the infection in the lung. Being unable to harmonize this conception of lobar pneumonia with the apparent beneficial effect of local pulmonary rest treatment and being somewhat skeptical of the supposition that the introduction of a relatively small amount of air into the pleural cavity really immobilizes the involved lobe through selective collapse, they attribute the beneficial results of pneumothorax treatment to a pleural stimulus which in some way mobilizes antibodies against infection. Anderson (16) also suggests that pneumothorax treatment may be followed by a flood of antibodies into the general circulation but regards this possibility as being due to a lessening of the flow of toxins from the compressed lung, thus permitting an excess of antibodies to appear.

The third theory, proposed by Holmes and Randolph (24), is dependent upon an acceptance of the theory of Coryllos and Birnbaum (25) concerning the pathogenesis of lobar pneumonia. According to this theory lobar pneumonia is primarily a pneumococcic infection of a bronchus resulting in occlusion of the bronchus by a tenacious plug of exudate. Following bronchial occlusion lobar atelectasis takes place, beginning at the periphery and progressing toward the hilum. Pneumococcic cellulitis proceeding peripherally ensues. If bronchial occlusion is relieved early, the disease is abortive, since clearing of the plugged bronchus precipitates the crisis, an event which usually occurs between the 5th and 8th days. On the basis of this conception Holmes and Randolph (24) suggest that it may be possible artificially to free

the plug by giving pneumothorax treatment, and thereby to induce an early crisis. At the same time through increase in intrapleural pressure spread of the infection from the hilum may be retarded.

#### EXPERIMENTAL OBSERVATIONS

In undertaking our own studies on the use of artificial pneumothorax in lobar pneumonia, now comprising observations on 42 cases, it seemed to us important from the beginning not only to have a working theory concerning the pathogenesis and pathology of the disease, particularly in its early stages, as a basis for interpretation of the means by which artificial pneumothorax might influence the morbid process, as others have done, but also to gather observations which might serve to answer some of the theoretical questions raised, as well as the more obvious practical question concerning the therapeutic usefulness of the procedure. While these observations have been gathered during the course of our studies, it seems desirable to present them here, reserving the observations on the effect of artificial pneumothorax on the clinical phenomena and course of the disease till later.

#### *Pathogenesis of lobar pneumonia*

Three major theories concerning the pathogenesis of lobar pneumonia have been referred to, namely, (a) that it is primarily a general infection with secondary hematogenous pulmonary localization, (b) that it is primarily a local, bronchogenic infection of the lung, the general manifestations of toxemia and bacteremia being secondary, and (c) that it is primarily a bronchogenic infection initiated by the occlusion of a bronchus with an infected plug of mucus with resulting lobar collapse and subsequent spread of the infection through the collapsed parenchyma.

The first theory that lobar pneumonia is hematogenous in origin has no experimental support, since attempts to produce the disease in normal animals by intravenous or subcutaneous inoculation of pneumococci have consistently failed (26, 27, 28, 29). Furthermore, it is difficult to harmonize the established fact that lobar pneumonia usually begins as a unilobar infection with a theory of hematogenous origin, since it would be expected that multiple foci of infection would develop more or less concomitantly throughout the lungs as does occur

in staphylococcal pneumonia of hematogenous origin and in miliary tuberculosis

The second theory that lobar pneumonia is bronchogenic in origin, is supported by the early experimental studies of Wadsworth (26), Armstrong (28), Lamar and Meltzer (30), Wollstein and Meltzer (31), and Winternitz and Hirschfelder (32) and would appear to have been firmly established in 1920 by the studies of Blake and Cecil (29) on experimental lobar pneumonia in monkeys, since they showed, following preliminary experiments by Opie, Freeman, Blake, Small, and Rivers (33) which demonstrated the susceptibility of this animal,<sup>3</sup> that the intratracheal introduction of minute amounts of pneumococcus culture consistently produced typical lobar pneumonia, while intravenous or subcutaneous inoculations consistently failed to do so in spite of the fact that a pneumococcemia of some days' duration ensued. Schobl and Sellards (34) have confirmed this result by finding that pneumonia could be experimentally produced in monkeys by intratracheal injection of pneumococci but not by intravenous inoculation, even though sterile broth or suspensions of killed pneumococci were injected intratracheally at the same time.

The third theory, advanced by Coryllos and Birnbaum (25), that lobar pneumonia is a bronchogenic infection initiated by bronchial occlusion with a plug of infected mucus with subsequent lobar collapse, is supported by them with experiments in dogs and by citation of a few human cases. On the other hand there would appear to be no convincing evidence that bronchial occlusion followed by lobar collapse commonly initiates lobar pneumonia in man.

Two series of observations have been made bearing on the moot theories of pathogenesis. The first consists of roentgenographic studies in 24 patients ranging in time from four to sixty hours after clinical onset of the disease. The second consists of intrapleural pressure determinations<sup>4</sup> on the same patients shortly after the x-ray films were taken. In the presence of lobar collapse resulting from

<sup>3</sup> The species of monkey is important. Lobar pneumonia clinically and anatomically comparable to the disease in man is most satisfactorily produced in *Pithecus philippinensis* Geoffroy (synonyms, *Macacus philippinensis* and *Macacus syrichtus*).

<sup>4</sup> All intrapleural pressure readings are expressed in centimeters of water and represent the true intrapleural pressure, i.e., the distance in centimeters between the water levels in the two arms of the manometer.



FIG 2 CASE 11 PRI TREATMENT ROENTGENOGRAM SHOWING COLLAPSE OF THE RIGHT LOWER LOBE AND SHIFT OF HEART TO THE RIGHT

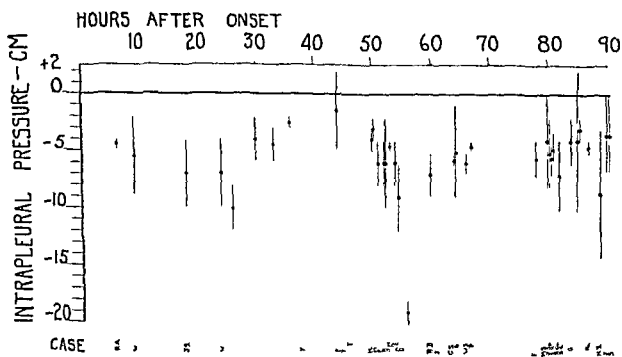


FIG 3 INTRAPLEURAL PRESSURE AT THE BEGINNING OF THE FIRST TREATMENT WITH ARTIFICIAL PNEUMOTHORAX IN 41 CASES OF LOBAR PNEUMONIA

bronchial occlusion in addition to the characteristic x-ray picture, the mean intrapleural pressure should be well below the normal range of  $-4$  cm to  $-8$  cm of water. In only one case in the series was the picture of bronchial occlusion with lobar collapse encountered (fig 2). In this one instance, case T F, a man, 47 years of age, with pneumonia of the right lower lobe, the disease was of 55 hours' duration, and consequently the phenomenon of lobar collapse may have been merely an incidental event, occurring during the course of the disease and without relation to its inception. In complete agreement with the roentgenographic observations, the only significantly low intrapleural pressure found was in the same case,  $-19$  cm, all other cases showing pressures within the normal range (fig 3). From these two series of observations it would seem clear that no evidence was obtained that bronchial occlusion with lobar collapse played any significant rôle in the pathogenesis of the pneumonia in this group of cases.

In view of these observations, together with the evidence provided by the experimental studies cited above, the second theory concerning the pathogenesis of lobar pneumonia would appear to be the most acceptable, namely, that it is a bronchogenic infection, the inception of which is not dependent upon the occlusion of a bronchus with an infected mucous plug.

#### *Evolution of the pneumonic lesion*

With respect to the evolution of the pneumonic process in lobar pneumonia several different views are held. The first, advanced by Weill and Mouriquand (35) and by Mason (36), who based their conclusions on roentgenographic studies of children with lobar pneumonia, holds that the lesion begins peripherally and spreads centrally. This view is supported by anatomical studies of lungs from fatal cases of pneumonia by Loeschke (37), who further believes that the initial peripheral infection spreads progressively to contiguous alveoli through the interalveolar pores of Kohn and to contiguous lobules through septal windows, primarily through the agency of the early inflammatory edema characteristic of pneumococcal infection (Rhoads and Goodner (38)) and secondarily by distribution of the infected edema fluid through the smaller air passages. Studies by Robertson, Coggeshall and Terrell (39, 40) on experimentally induced

lobar pneumonia in dogs support the foregoing conceptions to a considerable extent. The opposing view, advanced by Blake and Cecil (41, 42) and based by them on histological studies of lungs from monkeys with experimental and spontaneous lobar pneumonia either sacrificed or dying early in the disease, holds that the infection originates near the hilum and spreads peripherally by way of the perivascular, peribronchial and septal lymphatics and interstitial tissues and that hepatization begins near the hilum and progressively spreads more or less rapidly toward the periphery until complete lobar consolidation has developed. This view is supported by Sante (43) by means of serial roentgenographic studies of adults with lobar pneumonia. Experimental studies in rabbits by Permar (44) occupy an intermediate position, since they show that in this animal the process begins as a bronchial, atrial and alveolar lesion and that the infection spreads both peripherally and centrally by way of the interstitial tissues and lymphatics.

Evidence bearing on the foregoing questions concerning the pathology of lobar pneumonia is provided by roentgenographic films in 42 patients ranging in time from four to ninety hours after onset of the disease. These films show the evolution of the pneumonic process from its preconsolidative stage to the development of complete lobar consolidation in so far as it can be portrayed by the x-ray. They would appear to support the view that in adults, at least, the process of hepatization begins centrally and spreads peripherally. The largest series is from patients with pneumonia of the left lower lobe and comprises twenty films ranging in time from four to eighty-eight hours after onset. Six of these taken less than twenty-four hours after onset in the preconsolidative or very early consolidative stage, are shown in figure 4. None of them shows a peripheral lesion. Furthermore, they lend credence to the view that the infection is spreading peripherally by way of the tissues comprising the framework of the lung as shown by the appearance of the advancing margin of the lesion extending out from behind the cardiac shadow. One of the sixteen hour and the twenty-three hour roentgenograms are from the same patient, case W. L. The further evolution of the lesion to the development of complete consolidation of the left lower lobe is shown in figure 5.



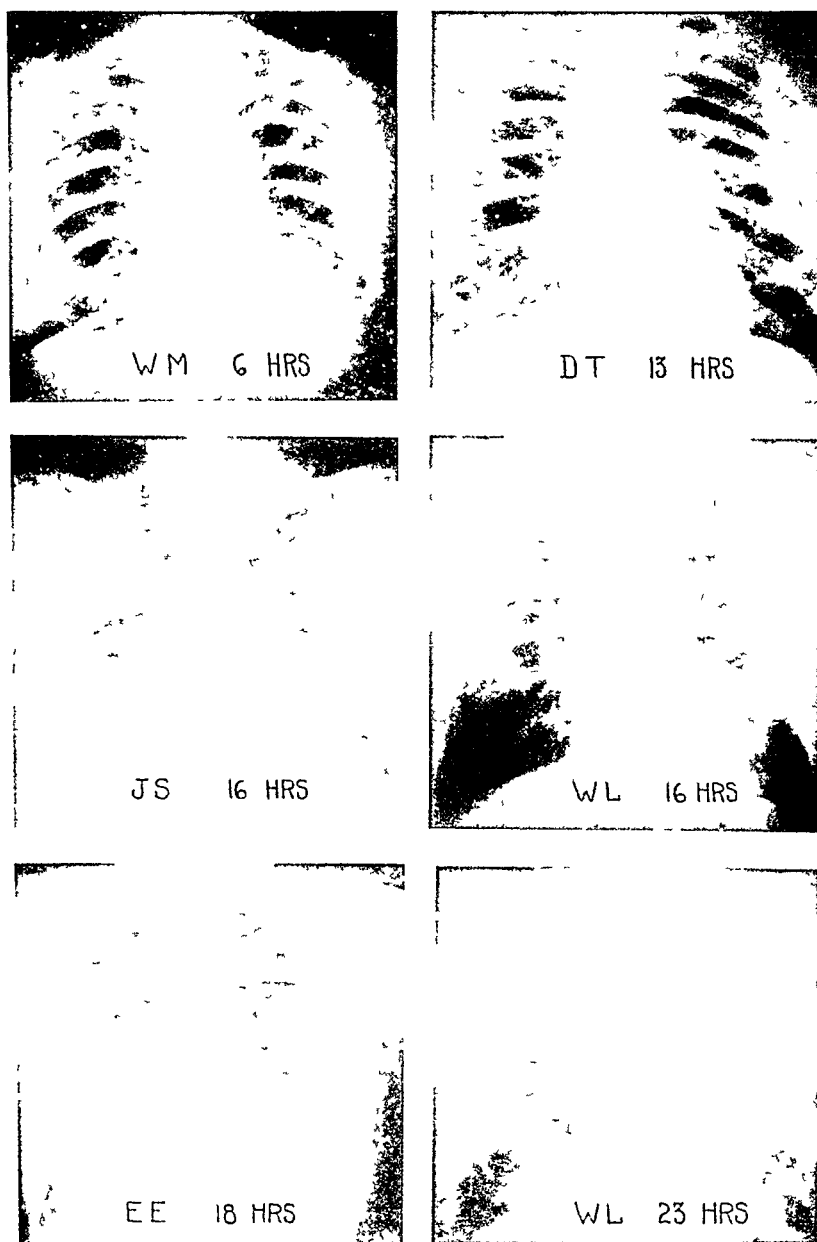


FIG 1 ROENTGENOGRAMS OF PATIENTS WITH LOBAR PNEUMONIA OF THE LEFT LOWER LOBE OF LESS THAN 24 HOURS' DURATION

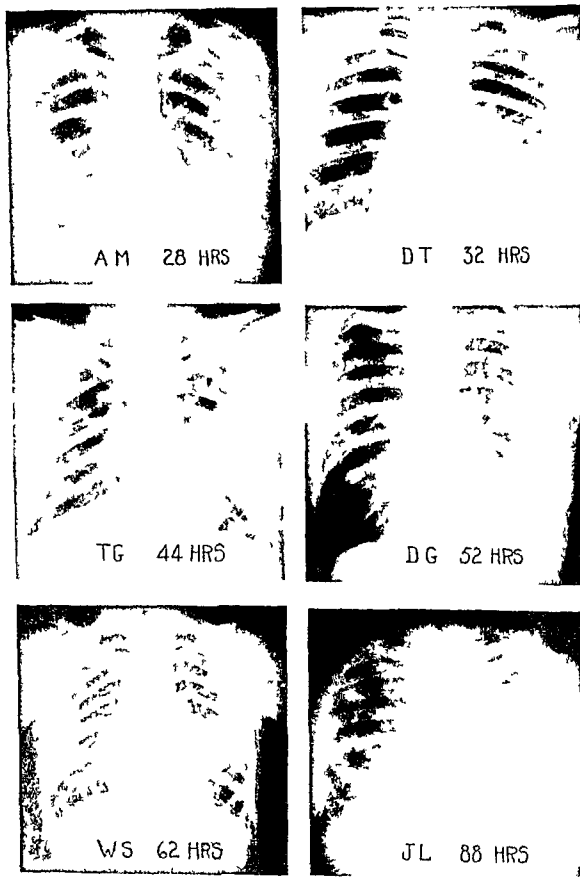


FIG. 5. ROENTGENOGRAMS OF PATIENTS WITH LOBAR PNEUMONIA OF THE LEFT LOWER LOBE OF 28 TO 88 HOURS' DURATION

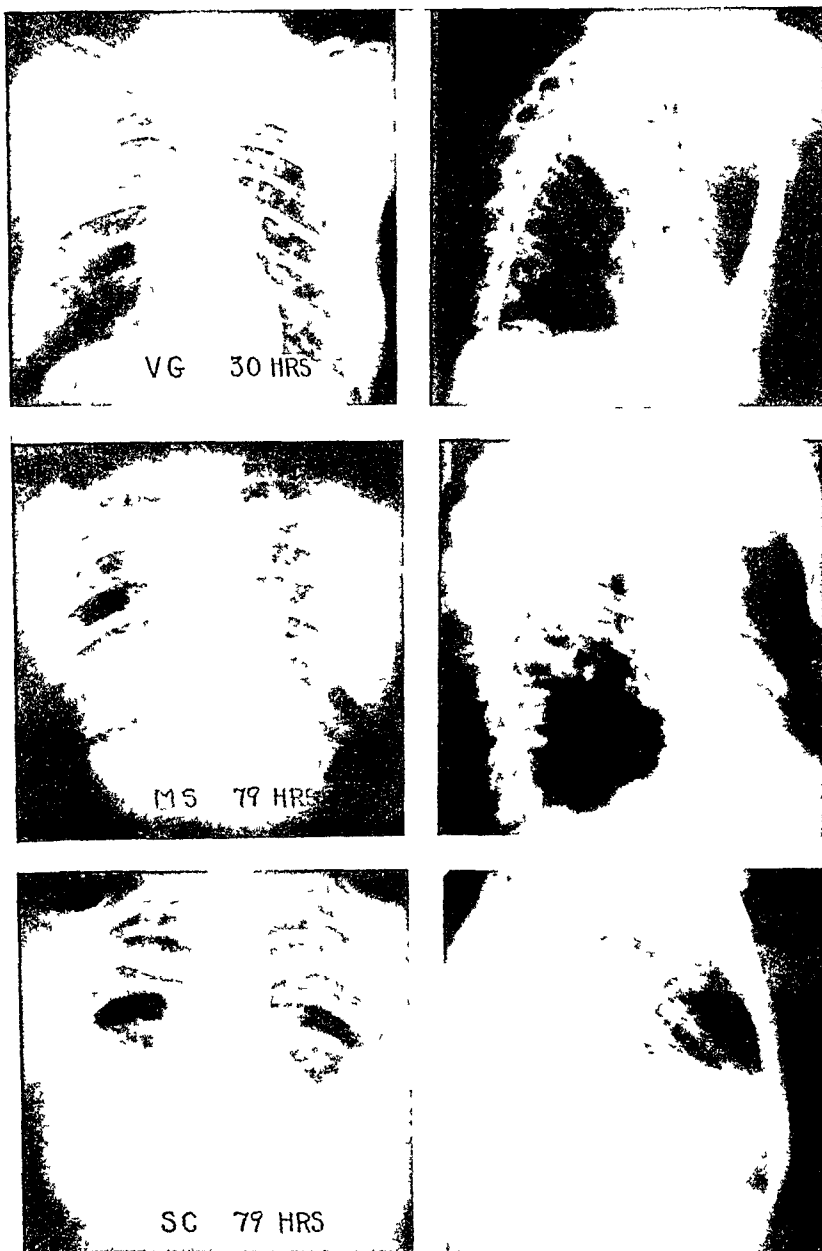


FIG 6 POSTEROANTERIOR AND LATERAL ROENTGENOGRAMS OF CASE V G, RIGHT UPPER LOBE, CASE M S, RIGHT MIDDLE LOBE, AND CASE S C, RIGHT LOWER LOBE

Further support for the view that hepatization ordinarily begins near the hilum and spreads peripherally is provided in figures 6, 7 and 8 by means of pairs of posteroanterior and lateral films from seven patients. The lateral films from cases V G (fig 6) and A W (fig 7) with pneumonia of the right upper and left upper lobes, respectively, show particularly well the illusory nature of the posteroanterior films,

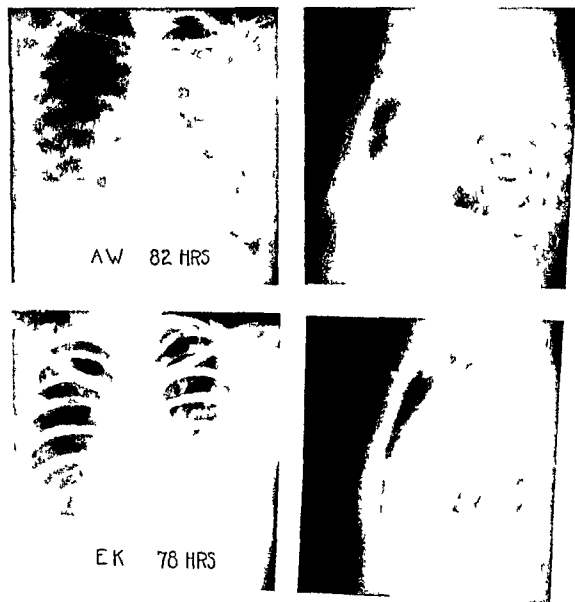


FIG 7 POSTEROANTERIOR AND LATERAL ROENTGENOGRAMS OF CASE A W, LEFT UPPER LOBE, AND CASE E K, LEFT UPPER LOBE

which taken by themselves would clearly suggest that the lesion was primarily peripheral and separated from the hilum by a zone of unconsolidated tissue

Not only do the roentgenographic studies appear to show that lobar pneumonia commonly begins centrally and spreads peripherally but they also indicate that the pneumonic process often develops first in

that portion of a lobe supplied by one of the larger bronchial branches, the remainder of the lobe supplied by the other larger branch or branches, as the case may be, becoming involved later in the disease. This is easily demonstrable in the right upper lobe in which that portion of the lobe supplied by the dorsolateral bronchi is nearly always involved first (fig 6, case V G ), that by the apical bronchi later

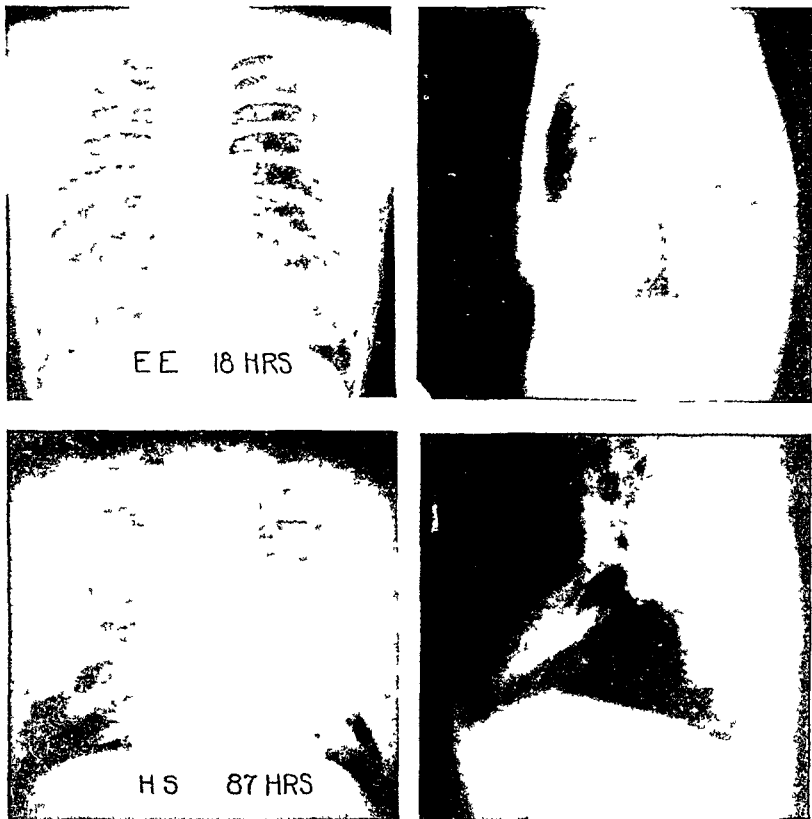


FIG 8 POSTEROANTERIOR AND LATERAL ROENTGENOGRAMS OF CASE E E, LEFT LOWER LOBE, AND CASE H S, LEFT LOWER LOBE

The same is true of the left upper lobe (fig 7, case A W ) Sometimes however, the portion of the left upper lobe supplied by the ventral bronchi, which corresponds to the middle lobe of the right lung (fig 6, case M S ), may be first involved (fig 7, case E K ) In pneumonia of the lower lobes the portion supplied by the inferior bronchial branches is usually involved first (fig 6, case S C , and fig 8, case E

E), that by the lateral branches later, although the reverse may occur (fig 8, case H S)

*Mechanism by which artificial pneumothorax exerts its effects*

It will be recalled that three major theories have been advanced to explain the apparent effects of artificial pneumothorax on the clinical phenomena and course of lobar pneumonia. Since the third of these, advanced by Holmes and Randolph (24), is based upon acceptance of Coryllos and Birnbaum's (25) theory of pathogenesis and the idea that dislodgement of a hypothetical plug of exudate from an occluded bronchus precipitates the crisis, it would hardly seem tenable at present in the absence of more definite supporting evidence and will not be discussed further here.

The second theory, namely that artificial pneumothorax accelerates the appearance of antibodies either through a hypothetical pleural stimulus or by shutting off absorption of antigen from the collapsed lobe is susceptible of study, since previous work by Dochez (45), Chickering (46), Blake (47) and many others, has shown that antibodies commonly appear in the blood in lobar pneumonia at or about the time of crisis. We have, therefore, made frequent, often daily determinations of the agglutinin titre of the serum for the homologous type of pneumococcus in 32 of the 42 cases of lobar pneumonia treated by artificial pneumothorax. The results of these studies are presented in table 1, from which it will be seen that there is no evidence in support of the theory that artificial pneumothorax accelerates the appearance of agglutinins in the blood, since only 4 of the 32 cases, which is no more than a normal expectancy, had developed agglutinins by the sixth day of the disease, and only 10 by the eighth. The theory that artificial pneumothorax accelerates recovery by stimulating or permitting an early development of humoral antibodies would, therefore, also appear to be untenable.

The first mentioned and most generally advocated theory, namely, that artificial pneumothorax exerts its influence by separating the inflamed pleural surfaces and immobilizing the acutely inflamed and constantly moving lung would *a priori* appear to be the most plausible. That the pleural surfaces are separated by the introduction of air into the pleural sac, provided there is no interference from adhesions, is

CASE	PNEUMO COCCUS TYPE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
R A	V	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
W M	IV	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
J S	XVIII	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
W L	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
R A	V	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
A T	VII	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
V	XII	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
G	V	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
E	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
T	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
H	II aty	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F	VII	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
C	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
J	VII	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
H	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
A	VII	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
C	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
G	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D	XXVIII	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
T	V	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
R	VIII	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D	V	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
J	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
B	II	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
G	VII	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
W	V	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
R	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
P	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F	VII	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
R	V	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M	V	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
S	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
J	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
E	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
K	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
C	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
S	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
H	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
S	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
R	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
P	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
A	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
N	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Agglutinin titer ± = 1 2, 1 4, + = 1 8, 1 16, ++ = > 1 16

S = Type I serum

D = died

Staggered line indicates day of pneumothorax treatment

easily demonstrable by roentgenographic study and is well established. To what extent the inflamed lung is immobilized by artificial pneumothorax as it has been employed by most who have used the method in the treatment of pneumonia, and whether or not a localized pneumothorax with selective collapse of the involved lobe occurs as contrasted with a mantle pneumothorax over the whole lung, apparently have not been studied nor has it been determined to what level the mean intrapleural pressure needs to be raised to accomplish immobilization.

At the beginning of our studies, then, an effort to determine whether selective collapse of the involved lobe took place following the introduction of relatively small amounts of air, was made. In the first

TABLE 2  
*Character of pulmonary collapse following 2 small pneumothorax treatments*

CASE	DAY	INVOLVED LOBE	AIR	RESULT
A C	3	R.L	650	Mantle pneumothorax, partial selective collapse of R L
J F	3	L.L	650	Mantle pneumothorax, greater collapse of L U
A M	2	L L	1100	Mantle pneumothorax, no selective collapse of L L
R D	3	R U	750	Mantle pneumothorax, no selective collapse of R U
F R	4	R U	600	Mantle pneumothorax, no selective collapse of R U

nine cases studied, five were without interfering pleural adhesions. In these five, x-ray films were taken before and after the introduction of relatively small amounts of air into the pleural cavity, amounts insufficient to cause complete collapse of the whole lung on the involved side. The results, shown in table 2, indicate that a mantle pneumothorax rather than selective collapse of the involved lobe occurred. In view of this the theory that selective collapse due either to decreased distensibility or to increased elasticity (Van Allen and Wu (48)) of the involved lobe would occur promptly in acute lobar pneumonia following the introduction of a relatively small amount of air into the pleural cavity, was abandoned and the establishment of complete collapse of the whole lung on the involved side was undertaken.



Subsequently roentgenographic and fluoroscopic studies were made to determine whether under these conditions expansion and contraction of the collapsed lung was abolished during respiration. At the same time the motion of the mediastinum, diaphragm, and thoracic cage and the relation of the position of the subject to these was investigated and compared with that in the normal, problems which have been previously studied extensively (49) in connection with the use of artificial pneumothorax in pulmonary tuberculosis but not in lobar pneumonia.

Three patients were studied in detail. The results are portrayed in diagrammatic form, the figures being traced directly from the x-ray films.

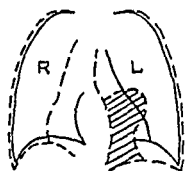
The first case, R. C., a High School boy of 18 with a Type VII pneumococcal lobar pneumonia of the left lower lobe, who had received four pneumothorax treatments totalling 3220 cc. of air, which was sufficient to cause complete collapse of the left lung, was studied in various positions four days after the last treatment, when convalescence was well established. At this time beginning re-expansion of the uninvolved left upper lobe was present while the involved left lower lobe was still completely collapsed. The observations made at this time were subsequently compared with similar observations made twelve weeks later on the same subject after the air had been completely absorbed and the thoracic organs were restored to their normal position. Figure 9 shows the position, with the subject in the upright and lateral positions, of the collapsed left lung, the heart, and the diaphragm in the presence of pneumothorax at both extremes of the respiratory cycle, superimposed upon the normal position of these organs in the same subject. It will be seen that in the upright position at the end of expiration the heart and collapsed lung are shifted well toward the right side and that the diaphragm, while showing the customary elevated expiratory position on the right, has failed to rise on the side of the pneumothorax. At the end of inspiration the heart has shifted back nearly to its normal position, the right half of the diaphragm has descended to the customary inspiratory position while the left half of the diaphragm has remained in the same position. This shift of the mediastinum toward the normal side with encroachment on the normal lung during expiration and its return during inspiration, contrary to frequently expressed opinions concerning the danger of

mediastinal displacement, should be of advantage to respiratory function as pointed out by Sewall (49) by assisting expulsion of air from the

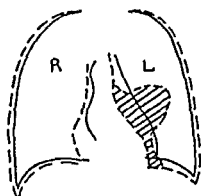
## MEDIASTINAL AND DIAPHRAGMATIC MOTION WITH RESPIRATION IN THE PRESENCE OF ARTIFICIAL PNEUMOTHORAX

### ERECT

#### EXPIRATION

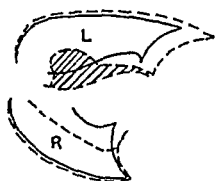


#### INSPIRATION

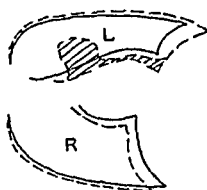


### ON RIGHT SIDE - COLLAPSED SIDE UP

#### EXPIRATION



#### INSPIRATION



— NORMAL —

— — WITH PNEUMOTHORAX — —

FIG 9 CASE R C, LOBAR PNEUMONIA, LEFT LOWER LOBE

Expiratory and inspiratory positions of heart, diaphragm and collapsed left lung in the presence of artificial pneumothorax with subject erect and on right side super imposed on normal positions in the same subject

normal lung during expiration and the intake of air during inspiration  
A similar shift of the heart to the right with expiration and return

toward the left with inspiration is exhibited with the patient lying in the lateral position with the pneumothorax side up

## EFFECT OF POSITION ON INTRAPLEURAL PRESSURE

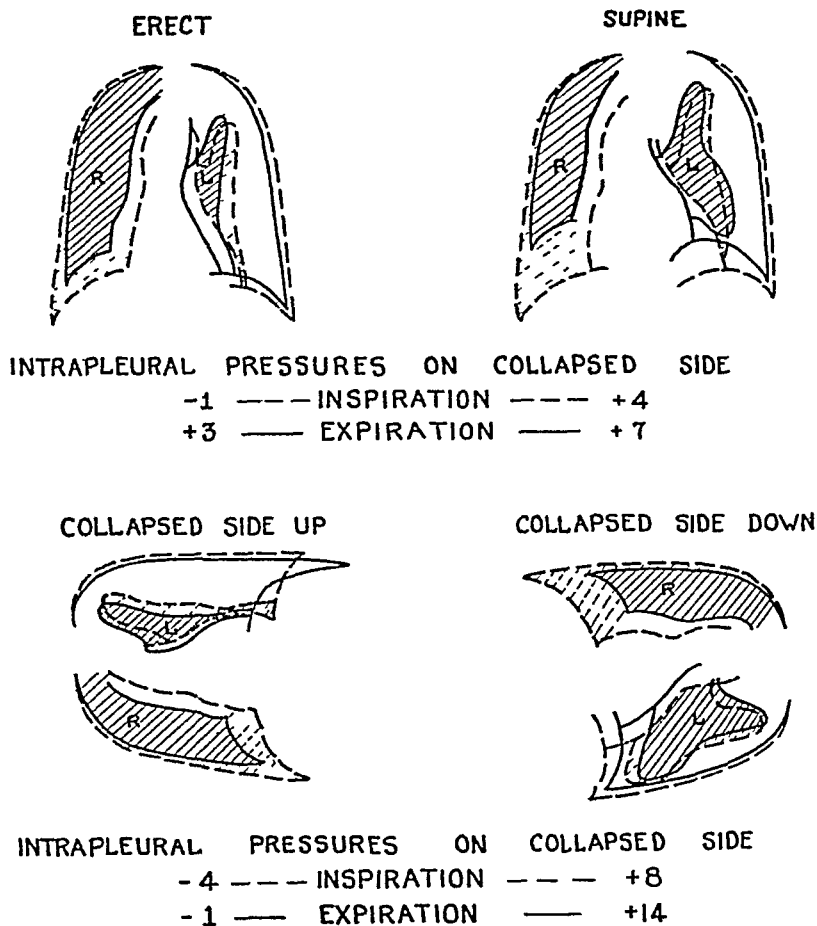


FIG 10 CASE R A, LOBAR PNEUMONIA, LEFT LOWER LOBE

Inspiratory and expiratory outlines of collapsed left lung, heart and diaphragm with subject in various positions, showing respiratory immobilization of collapsed lung and effect of position on intrapleural pressure

Of particular importance in relation to the problem in hand is the fact that the completely collapsed pneumonic left lower lobe neither under fluoroscopic observation nor in the x-ray films showed any evidence of expansion with inspiration nor of contraction with expiration,

a fact which stands out more clearly in diagrams from the next case in which the films taken at the end of inspiration and at the end of expiration with the subject in various positions are superimposed (fig 10) In this case, R A , a college student of 20, with pneumococcal Type V lobar pneumonia of the left lower lobe of 6 hours duration, studies were made about 36 hours after the introduction of 2600 cc of air in two treatments of 2000 and 600 cc respectively, at which time the left lung was completely collapsed, the temperature was normal and the patient convalescent While the collapsed left lung, as would be expected, alters its position in the thoracic cavity synchronously with changes in the position of the mediastinum occurring with expiration and inspiration and with change in bodily position, there is no expansile motion of the lung with inspiration nor contractile motion with expiration and in this important sense the lung may be said to be completely immobilized when completely collapsed The mechanism involved in this immobilization is relatively simple and would appear to depend upon the balance of opposing forces concerned with expansion and contraction of the lung during respiration The initial collapse of the lung when air is introduced into the pleural cavity is, of course, due to its elasticity and becomes complete when the opposing force, i e , the pressure differential between the alveolar spaces and the pleural sac, which normally is sufficient to keep the lung distended and the visceral and parietal pleurae in constant apposition, is abolished by the introduction of a sufficient amount of air into the closed pleural sac Under these circumstances the fall in pressure with inspiration is sufficient to permit the displaced mediastinum to return toward its normal position but the pressure differential developed when the subject is in the lateral position with pneumothorax side up and the pressure falls into the negative zone, would nevertheless appear to be inadequate to overcome immediately the elastic force and perhaps inertia of the lung

The foregoing observations show that the lung can be immobilized in lobar pneumonia and clearly support the theory that artificial pneumothorax exerts its influence by limiting or abolishing the constant expansile and contractile motion of the involved lung during respiration

*Factors influencing the volume and frequency of pneumothorax treatments required to immobilize the pneumonic lung*

In attempting to determine the amount of air to be introduced and the level to which the mean intrapleural pressure needs to be raised to induce complete collapse and immobilization of the lung, it quickly became evident that a number of variables such as the duration of the disease, the side and extent of the lesion, the size of the thoracic cage and the presence or absence of fibrous pleural adhesions had to be taken into account. Even more important than these, however, is the position of the patient, a problem which has been studied in a few cases of tuberculosis by Lawson (50). Consequently detailed studies of this variable have been made in a series of patients. One of these studies on case R. A., made at the same time as the roentgenographic observations portrayed in figure 10, is characteristic of them all. It will be seen that the intrapleural pressure of  $-1 + 3$  cm. with the subject in the erect position rose to  $+4 + 7$  cm. when he lay on his back, fell to  $-4 - 1$  cm. when he lay on his side with the collapsed side up, and rose to a high level,  $+8 + 14$  cm., when he was in the reverse position with the collapsed side down. A similar study of the effect of position on intrapleural pressure is shown in figure 11, the pressure readings in this instance being recorded kymographically by means of a capsule and lever attached to the open end of the manometer. The patient, H. K., with pneumonia of the right lower lobe of 36 hours' duration at the time of the first pneumothorax treatment received three treatments totalling 2850 cc. within a period of 20 hours. The observations were made about 21 hours after the last treatment. With the subject on his back breathing naturally the mean intrapleural pressure was  $+5$  cm. When he changed to an upright position it fell to  $+3$  cm., to rise to  $+5$  cm. again when he returned to the supine position. In the lateral position with the pneumothorax side up it was  $\pm 0$  cm., with the pneumothorax side down  $+8$  cm., then  $+6$  cm., following a short period of deep breathing. These and similar studies in other patients indicate that in order to obtain and maintain complete collapse and immobilization of the pneumonic lung, the mean intrapleural pressure should ordinarily be raised to at least  $+1$  cm. if the patient is lying with his pneumonic side up, to  $+4$  cm. to  $+5$  cm. if he is lying on his back.

Other possible factors besides position, such as site and duration of the pneumonia and presence or absence of adhesions may conceivably influence the volume of air required to raise the mean intrapleural pressure to a positive level. Consequently, study of the rise in intrapleural pressure during pneumothorax treatment has been made in nearly all of the 42 cases treated by recording expiratory, inspiratory and mean intrapleural pressures after each 50 to 100 cc of air introduced together with the rate of air intake. The records of the first treatment in three cases and of the first and second treatments in a fourth case, all comparable with respect to the site and duration of the pneumonia and

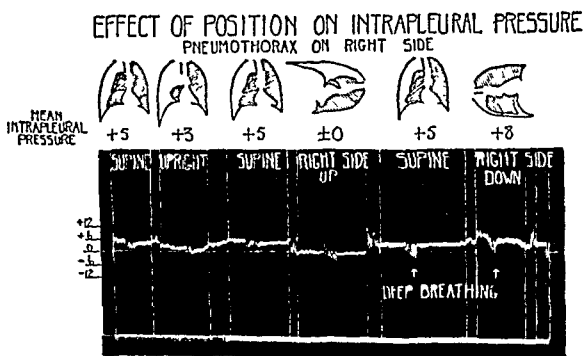


FIG 11 CASE H K, LOBAR PNEUMONIA WITH ARTIFICIAL PNEUMOTHORAX, RIGHT LOWER LOBE. EFFECT OF CHANGE IN POSITION ON MEAN INTRAPLEURAL PRESSURE

position during treatment, since all four were cases of pneumonia of the left lower lobe treated in the first 24 hour period after onset and in the lateral position with the pneumonic side up, are shown in figure 12. Case R A, a young man of 20, received 2000 cc of air during the first treatment at a relatively slow rate averaging 19.4 cc per minute. The respirations were shallow, the mediastinum was freely movable, the rise in intrapleural pressure was relatively slow, 1700 cc of air being required to bring the mean pressure to atmospheric level. Case W M, a man of 63, with a relatively fixed mediastinum and a much greater respiratory swing in pressure, took in air at a faster average

rate of 32.5 cc per minute and required 1200 cc to bring his mean intrapleural pressure to atmospheric level Case J S , a man of 45, with extensive adhesions between the parietal and visceral pleura over the left upper lobe, taking in air at an average rate of only 10.5 cc per minute showed a rapid rise in intrapleural pressure, the mean pressure having reached atmospheric level after only 650 cc of air had been introduced Case W L , a man of 32, without pleural adhesions, in two treatments with an interval of 3 hours 45 minutes between them,

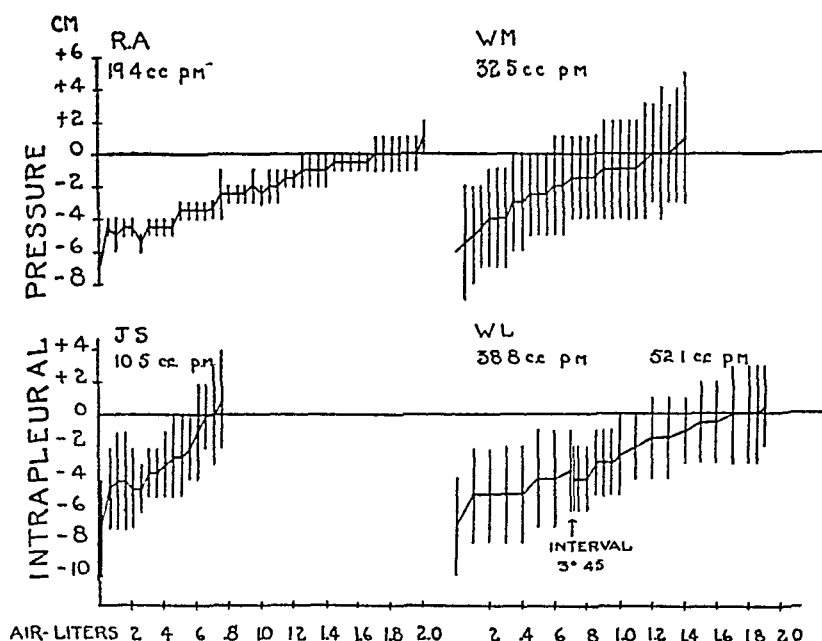


FIG 12 RISE IN INTRAPLEURAL PRESSURE DURING INTRODUCTION OF AIR INTO PLEURAL CAVITY IN 4 CASES OF LOBAR PNEUMONIA OF THE LEFT LOWER LOBE

required 1700 cc of air to raise the mean intrapleural pressure to atmospheric level, the same amount as in case R A , but air was introduced at a much more rapid rate, 38.8 cc per minute during the first treatment, 52.1 cc per minute during the second treatment

These four cases serve to indicate a few of the many variables which play a part in determining the volume of air required to raise the mean intrapleural pressure to the desired point of +1 cm In fact, a careful analysis of all our records indicates that the variables are so numerous and immeasurable that no definite correlation can be established

between the volume of air required and any other factor. Similar studies made during refill treatments likewise have failed to show correlation between the volume of air required to maintain intrapleural pressure at the desired level and any other measurable factor.

Knowledge with respect to the rate at which intrapleural pressure falls following the initial treatment is desirable as a basis for determining the frequency with which refills should be undertaken in order to keep the mean intrapleural pressure positive and the lung im-

### FALL IN INTRAPLEURAL PRESSURE AFTER FIRST TREATMENT

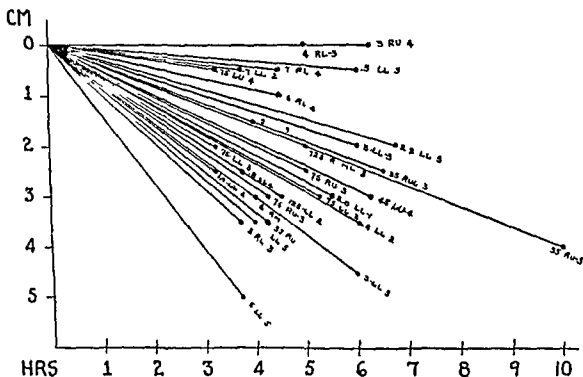


FIG 13 RATE OF FALL IN INTRAPLEURAL PRESSURE FOLLOWING FIRST PNEUMOTHORAX TREATMENT IN 29 CASES OF LOBAR PNEUMONIA

3 RU-4, etc indicate 300 cc of air given in first treatment, pneumonia of right upper lobe, fourth day of disease

bilized. This has been analyzed in 29 cases for time intervals ranging from  $3\frac{1}{4}$  to 10 hours between the first and second treatments, the volume of air introduced in the first treatment having varied from 300 to 2200 cc. The data presented in figure 13 indicate that there is wide individual variation and no predictable relationship between the rate of fall and the volume of air introduced, the site of the lesion or the duration of the disease. Similar studies of the rate of fall in intrapleural pressure between subsequent refills (fig 14) show a similar



individual variation uncorrelated with the total volume of air introduced. The rate of fall, however, is in general less rapid than between the first and second treatments, the median rate after the first treatment being about 0.52 cm per hour, after subsequent treatments about 0.27 cm per hour. Occasionally an interval rise in intrapleural pressure is encountered, an indication that a pleural effusion may be developing.

## FALL IN INTRAPLEURAL PRESSURE

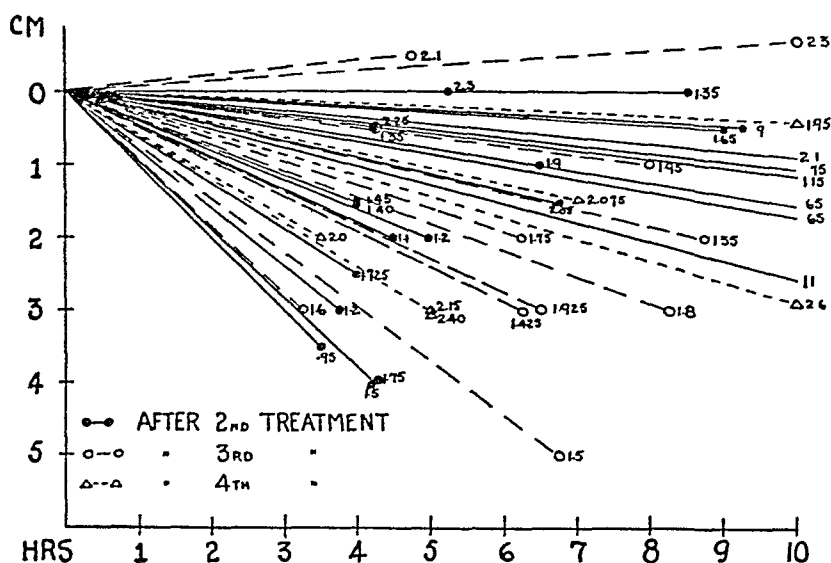


FIG 14 RATE OF FALL IN INTRAPLEURAL PRESSURE FOLLOWING SECOND, THIRD, AND FOURTH PNEUMOTHORAX TREATMENTS

Numbers (21, etc) indicate total amount of air in liters administered in previous treatments

## Summary

The foregoing observations, briefly summarized, would appear to support the following views:

1. Lobar pneumonia is a bronchogenic infection beginning as an acute inflammatory lesion at the site of pneumococcal invasion at or near the hilum of the lung, usually unilaterally and in one lobe and without bronchial occlusion as an initiating event. The infection spreads rapidly from the hilum toward the periphery frequently first

through one section of a lobe, subsequently through the remainder. This spread is fostered no doubt by the spreading inflammatory edema and perhaps peculiarly facilitated by the constant expansion and contraction of the lung in respiration. Hepatization begins in the hilar portion of the lobe and progresses toward the periphery. The rate at which consolidation develops varies considerably in different cases but ordinarily requires from 50 to 70 hours to become relatively complete.

2 In the pre-consolidative and early consolidative stages the inflamed lobe readily collapses following the introduction of air into the pleural cavity, but not selectively, the pneumothorax separating the pleural surfaces and mantling the whole lung, provided preexisting fibrous pleural adhesions do not interfere.

3 There is no evidence to support the view that artificial pneumothorax exerts a beneficial therapeutic effect by accelerating or enhancing the production of antibodies nor by expelling bronchial exudates and draining the lung of inflammatory products. On the other hand, complete immobilization of the lung so far as respiratory expansion and contraction are concerned can be attained by suitable pneumothorax therapy. Consequently the "lung rest theory" would appear to be the most acceptable one at present, even though no evidence has been developed as yet to show in what manner collapse and immobilization of the pneumonic lung, apart from relief of pleural pain, serves to exert a beneficial influence.

4 To attain complete immobilization of the lung so far as respiratory expansion and contraction is concerned a sufficient amount of air must be introduced to cause complete collapse. To accomplish this the mean intrapleural pressure should be raised to at least +1 cm of water when the patient is in the lateral position with the pneumonic side up, +4 to +5 cm if he is in the supine position and is to be allowed to lie on his uninvolved side.

5 The volume of air required to accomplish complete collapse varies greatly from case to case and cannot be definitely correlated with any measurable factors nor can it be predicted. It ordinarily varies from 1800 to 2400 cc.

6 The rate of fall in intrapleural pressure following the initial treatment is also very variable and unpredictable, ranging from 0 to 1.33 cm per hour in the cases studied. The rate of fall following re-

fills is likewise variable, ranging from none to 1 cm per hour, though it is commonly less rapid than after the first treatment. Consequently the frequency and volume of refills required to maintain immobilization of the lung is at present empirical.

#### THERAPEUTIC EFFECTS OF ARTIFICIAL PNEUMOTHORAX

Our observations on the effect of artificial pneumothorax on the clinical phenomena and course of lobar pneumonia are based upon the treatment of 42 cases<sup>5</sup> over a period of 16 months. All patients with unilateral lobar pneumonia admitted to the Medical Service of the New Haven Hospital not later than the third calendar day of the disease during this period have been treated without selection, 24 in all. The remaining 18 patients were arbitrarily selected cases in whom treatment was begun on the fourth day in 16, on the fifth day in 2. In addition to the usual clinical records the observations include serial postero-anterior and lateral roentgenograms at frequent intervals throughout the acute and convalescent periods, repeated measurements of intrapleural pressure, and serial blood cultures, titrations of humoral antibodies and leukocyte counts.

The data concerning these cases, to be found in tables 3 to 6, may be summarized briefly. There were 31 males and 11 females. Their ages ranged from 13 to 77, 4 being in the second decade of life, 9 in the third, 13 in the fourth, 10 in the fifth, 4 in the sixth, 1 in the seventh and 1 in the eighth. Thirty-eight cases were unilobar, of which 18 had right-sided pneumonia (upper lobe 8, middle lobe 1, lower lobe 9), 20 left-sided pneumonia (upper lobe 3, lower lobe 17). Four cases were multilobar, of which 3 were right-sided, 1 bilateral. The distribution of cases according to the type of pneumococcus was as follows: Type I, 18, Type II, 1, Type II atypical, 1, Type V, 7, Type VII, 4, Type VIII, 2, Type XII, 1, Type XVIII, 2, Type XXVIII, 1, Group IV, not further classified, 3, undetermined, 2. Bacteremia was present in 7 cases at the time pneumothorax treatment was instituted. Twenty-three cases were found to have more or less extensive pleural adhesions, of which 15 had a definite past history of pneumonia or pleurisy, while of 16 cases without pleural adhesions only 4 had a past history of

<sup>5</sup> Treatment was attempted in 3 additional cases but extensive pleural adhesions prevented the introduction of air into the pleural cavity.

pneumonia or pleurisy and in 2 of these it was known to have been on the contralateral side

### *Method of treatment*

The procedure followed with respect to the frequency and volume of pneumothorax treatments has been evolutionary and empirical and is illustrated in figure 15. At the beginning it was hoped that a selective collapse of the involved lobe induced by means of two initial treatments of approximately 300 to 500 cc each, given 6 hours apart, followed if necessary by a third treatment 18 hours later, might be sufficient to accomplish the desired result and this appeared to be the case in the first two cases treated, one of which is illustrated by case A C, fig 15. It soon became evident, however, as previously stated, that selective collapse did not occur. Furthermore, by the time 9 cases had been treated it had become apparent that this procedure was inadequate since, as illustrated by case A M (fig 15), following temporary clinical improvement relapse was liable to occur as the intrapleural pressure fell, provided antibodies had not appeared in the blood as was subsequently found to have happened in the first two patients showing prompt recovery. At the same time the first hint was obtained that preexisting fibrous pleural adhesions (cases H T, table 4, and D G and W S, table 5) might interfere with the usefulness of artificial pneumothorax and that the procedure would probably be of no value in advanced septicemic cases (case J G, table 6).

In view of these results the procedure was changed as illustrated by case V G, fig 15. Three to five initial treatments were given at approximately four hour intervals until sufficient air had been introduced to establish a positive expiratory intrapleural pressure with a mean pressure in the neighborhood of +1 to +2 cm of water, resulting in a complete collapse of the whole lung on the involved side. The first three treatments were ordinarily of 500 to 800 cc each. The total amount of air introduced in these initial treatments ranged from 1700 to 2625 cc, provided extensive adhesions did not interfere. Subsequent treatments were given at irregular intervals in an effort to maintain a positive intrapleural pressure and complete collapse and immobilization of the lung until permanent recovery seemed assured or further treatment inadvisable. Twenty patients were treated

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Our observations on the effect of artificial pneumothorax on the clinical phenomena and course of lobar pneumonia are based upon the treatment of 42 cases<sup>5</sup> over a period of 16 months. All patients with unilateral lobar pneumonia admitted to the Medical Service of the New Haven Hospital not later than the third calendar day of the disease during this period have been treated without selection, 24 in all. The remaining 18 patients were arbitrarily selected cases in whom treatment was begun on the fourth day in 16, on the fifth day in 2. In addition to the usual clinical records the observations include serial postero-anterior and lateral roentgenograms at frequent intervals throughout the acute and convalescent periods, repeated measurements of intrapleural pressure, and serial blood cultures, titrations of humoral antibodies and leukocyte counts.

The data concerning these cases, to be found in tables 3 to 6, may be summarized briefly. There were 31 males and 11 females. Their ages ranged from 13 to 77, 4 being in the second decade of life, 9 in the third, 13 in the fourth, 10 in the fifth, 4 in the sixth, 1 in the seventh and 1 in the eighth. Thirty-eight cases were unilobar, of which 18 had right-sided pneumonia (upper lobe 8, middle lobe 1, lower lobe 9), 20 left-sided pneumonia (upper lobe 3, lower lobe 17). Four cases were multilobar, of which 3 were right-sided, 1 bilateral. The distribution of cases according to the type of pneumococcus was as follows: Type I, 18, Type II, 1, Type II atypical, 1, Type V, 7, Type VII, 4, Type VIII, 2, Type XII, 1, Type XVIII, 2, Type XXVIII, 1, Group IV, not further classified, 3, undetermined, 2. Bacteremia was present in 7 cases at the time pneumothorax treatment was instituted. Twenty-three cases were found to have more or less extensive pleural adhesions, of which 15 had a definite past history of pneumonia or pleurisy, while of 16 cases without pleural adhesions only 4 had a past history of

<sup>5</sup> Treatment was attempted in 3 additional cases but extensive pleural adhesions prevented the introduction of air into the pleural cavity.

pneumonia or pleurisy and in 2 of these it was known to have been on the contralateral side

### *Method of treatment*

The procedure followed with respect to the frequency and volume of pneumothorax treatments has been evolutionary and empirical and is illustrated in figure 15. At the beginning it was hoped that a selective collapse of the involved lobe induced by means of two initial treatments of approximately 300 to 500 cc each, given 6 hours apart, followed if necessary by a third treatment 18 hours later, might be sufficient to accomplish the desired result and this appeared to be the case in the first two cases treated, one of which is illustrated by case A C, fig 15. It soon became evident, however, as previously stated, that selective collapse did not occur. Furthermore, by the time 9 cases had been treated it had become apparent that this procedure was inadequate since, as illustrated by case A M (fig 15), following temporary clinical improvement relapse was liable to occur as the intrapleural pressure fell, provided antibodies had not appeared in the blood as was subsequently found to have happened in the first two patients showing prompt recovery. At the same time the first hint was obtained that preexisting fibrous pleural adhesions (cases H T, table 4, and D G and W S, table 5) might interfere with the usefulness of artificial pneumothorax and that the procedure would probably be of no value in advanced septicemic cases (case J G, table 6).

In view of these results the procedure was changed as illustrated by case V G, fig 15. Three to five initial treatments were given at approximately four hour intervals until sufficient air had been introduced to establish a positive expiratory intrapleural pressure with a mean pressure in the neighborhood of +1 to +2 cm of water, resulting in a complete collapse of the whole lung on the involved side. The first three treatments were ordinarily of 500 to 800 cc each. The total amount of air introduced in these initial treatments ranged from 1700 to 2625 cc, provided extensive adhesions did not interfere. Subsequent treatments were given at irregular intervals in an effort to maintain a positive intrapleural pressure and complete collapse and immobilization of the lung until permanent recovery seemed assured or further treatment inadvisable. Twenty patients were treated

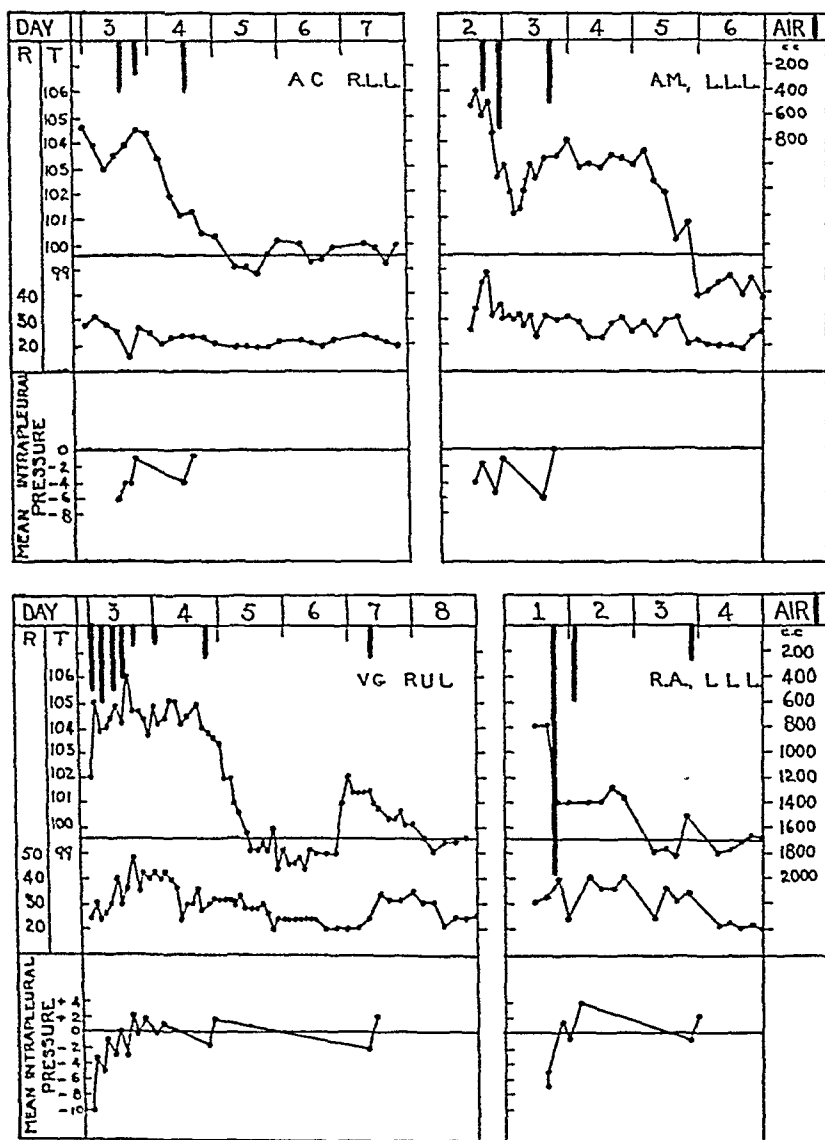


FIG 15 CASES ILLUSTRATING CHANGE IN METHOD OF TREATMENT AS STUDY OF THE USE OF ARTIFICIAL PNEUMOTHORAX IN LOBAR PNEUMONIA PROGRESSED

Case A C, first case treated, partial collapse of right lung, critical recovery Case A M, fifth case treated, partial collapse of left lung, temporary improvement with relapse Case V G, eleventh case treated, complete collapse of right lung, transient rise in temperature with falling intrapleural pressure on seventh day. Case R A, fortieth case treated, complete collapse of left lung, prompt recovery without relapse

under this plan. Gradually a further modification of procedure was tried in which the initial treatment was increased in amount and the early refills were given at somewhat less frequent intervals, a method which appears to present distinct advantages. This procedure as used in 6 recent cases is illustrated by case R A, fig 15.

The technique employed has been that commonly used and requires no detailed comment. Immediately following the preliminary examination of the patient an x-ray film of the chest is taken to confirm the clinical diagnosis and to make certain that the pneumonia is unilateral. Following a preliminary dose of morphine, artificial pneumothorax treatment is started. Treatments are ordinarily given with the patient in the lateral position, pneumonic side up, since the intrapleural pressure established with the subject in this position does not become lower in any other position which he may subsequently take (fig 11). Following preparation with novocaine, the needle is commonly inserted in the mid or posterior axillary line, fourth to sixth intercostal space, or near the lower angle of the scapula, an effort being made to avoid areas showing the physical signs of acute fibrinous pleurisy. Air is allowed to flow in under the negative pressure developed during inspiration until the intrapleural pressure has nearly reached the atmospheric level, when a slightly positive pressure is used. The rate of introduction of air is a matter of considerable importance, especially in the use of the large initial treatments, if increased respiratory rate and dyspnea are to be avoided. With increasing experience the rate has been gradually cut down from an average rate of approximately 20 to 40 cc per minute used at first to 10 to 20 cc per minute. At this latter rate, which is now used, large amounts can apparently be administered in the initial treatment without difficulty. Pressure readings are taken after every 50 to 100 cc of air introduced. If, during the treatment, the patient complains of a dragging or pulling pain, adhesions may be suspected and the treatment may be interrupted. Following the first, second, or third treatment another x-ray film is taken to determine the degree of collapse of the lung and the presence or absence of pleural adhesions.

#### *Clinical results*

The effect of artificial pneumothorax treatment on individual clinical phenomena of lobar pneumonia is difficult or impossible to



measure or evaluate with accuracy, at least, in our series of cases because of the fact that the procedure employed has been gradually modified as we have proceeded

In general terms, however, it may be said that pleural pain has been quickly and effectively relieved or abolished in nearly all patients in whom pleural adhesions have not interfered with adequate separation of the pleural surfaces; that in the cases who have responded to the treatment dyspnea has been relieved in most instances, and the toxic and apprehensive appearance has been strikingly improved. No abrupt fall in the leukocyte count has occurred except in 3 cases, the majority showing a gradual return to the normal level over a period of 2 to 5 days. In none of the seven septicemic cases did artificial pneumothorax exert any apparent influence on the blood stream infection, while in four cases (F H, E E, and T G, table 4, and R P, table 5), a transient bacteremia occurred following artificial pneumothorax treatment and in one case (F M, table 5), uninfluenced by pneumothorax treatment, a terminal septicemia developed. No studies have been made as yet concerning the possible influence of artificial pneumothorax on the anoxemia of lobar pneumonia, though our tentative impression would be that the effect on cyanosis roughly parallels that on dyspnea.

Since an analysis of the effect of artificial pneumothorax on the clinical course and outcome of lobar pneumonia in the 42 cases treated indicates that the duration of the disease at the time treatment was instituted, as well as the method of treatment used, was one of the most important factors influencing the results obtained, the cases have been grouped according to duration for purposes of presentation. Duration in hours after onset has been selected as the basis for grouping, since it would appear to be of greater significance than the calendar day of the disease. Group A comprises 4 cases in whom treatment was begun within 24 hours after onset, Group B 9 cases in whom treatment was started between 24 and 48 hours after onset, Group C 15 cases in whom treatment was initiated between 48 and 72 hours after onset, and Group D 14 advanced cases of more than 72 hours' duration when treatment was begun. Another important factor which apparently influenced the results in Groups B and C at least, was the absence or presence of preexisting fibrous pleural adhesions. Consequently these two groups have been subdivided accordingly.

*Group A Treatment begun within 24 hours after onset* Summarized data concerning the 4 cases in this group are shown in table 3. It will be seen that all four cases were treated with large initial amounts of air which resulted in raising the mean intrapleural pressure to a positive level. Complete collapse of the whole left lung occurred in all except case J S, in whom adhesions between the parietal and visceral pleura over the uninvolved upper lobe prevented collapse of this lobe. All four cases recovered promptly without further extension of the pneumonia and without complications except for a transient acute psychosis in case W L, a severe chronic alcoholic. The individual case records with brief clinical notes are presented on pages 38-39.

*Group B Treatment begun between 24 and 48 hours after onset* Data concerning the 9 cases in this group subdivided into a group of 6 cases without pleural adhesions and a group of 3 with adhesions, are shown in table 4. In the 6 cases without adhesions all except case A M, who was one of the early inadequately treated cases, received initial treatments sufficient in volume to raise the mean intrapleural pressure to atmospheric level or above and to collapse the whole lung on the involved side. All showed prompt clinical improvement with relief of distressing symptoms except case F H, presumably because he also suffered from rheumatic heart disease with cardiac dyspnea of some months duration and a bout of transient auricular fibrillation. Recovery was rapid in case H K, apparently accelerated in all with the possible exception of case R F, who nevertheless was much improved symptomatically. None showed further spread of the pneumonia. Two developed sterile pleural effusions which were sufficiently large to warrant withdrawal by aspiration.

In the 3 cases with pleural adhesions no notable effect on the symptoms or course of the disease occurred under pneumothorax treatment, presumably because the adhesions interfered with adequate collapse and immobilization of the lung, even though the mean intrapleural pressure was raised to a positive level in cases E E and T G. All 3 cases recovered without spread of the pneumonia to other lobes and without complications.

The individual records of the cases in Group B are presented on pages 38-39.

*Group C Treatment begun between 48 and 72 hours after onset* The 15 cases in this group, 6 without pleural adhesions and 9 with

adhesions, are summarized in table 5 Of the 6 cases without adhesions 4 recovered promptly by crisis One of these, case T F., who

*Cases treated in preconvulsion*

CLINICAL DATA							PNEUMONIA			
Case	Sex	Age	Pneumococcus type	Blood cultures	Site	Pleural adhesions	Begun		Initial	
							Hours after onset	Calendar day	Number of treatments	Amount of air
R A	M	20	V	—	L L	±	6	1	2	cc 2,600
W M	M	63	IV	—	L L	—	9	2	4	2,150
J S	M	45	XVIII	—	L L	+	18	2	4	2,200
W L*	M	32	I	—	L L	—	24	2	4	2,625

\* Severe alcoholic † In this and subsequent tables, — = no agglutinins developed, ? indicates agglutinins may have been present

*Cases in which treatment was attempted*

CLINICAL DATA							PNEUMONIA			
Case	Sex	Age	Pneumococcus type	Blood cultures	Site	Pleural adhesions	Begun		Initial	
							Hours after onset	Calendar day	Number of treatments	Amount of air
R F	M	20	V	—	L L	—	26	2	5	cc 2,300
A M	F	33	I	—	L L	—	30	2	2	1,100
V G	F	30	I	—	R U	—	31	3	5	2,150
D T	M	21	VII	—	L L	—	33	2	4	2,500
H K	M	23	?	—	R U	—	36	2	3	2,850
F H*	M	39	XII	—+—	R U M L	—	38	3	3	2,025
E E†	F	33	V	—+—	L L	++	44	3	4	1,075
T G	M	49	I	—+—	L L	++	45	3	4	1,950
H T	M	36	II aty	—	R U L	++	46	3	3	1,000

\* Rheumatic heart disease † Initial treatment attempted on second day failed because of adhesions but resulted in a partial recovery

has been referred to as the one case in the series showing evidence of bronchial occlusion and lobar atelectasis, had two subsequent transient

elevations of temperature unaccompanied by other symptoms The other three, cases A C, R D and J F, who were among the early

within 24 hours after onset

TREATMENTS				RESULT				
Maintenance refills		Total		Clinical course following treatment	Calendar day	Agglutinins first appeared day	Spread to other lobes	Complications
Number of treatments	Amount of air	Number of treatments	Amount of air					
	cc		cc					
1	300	3	2 900	Prompt recovery by rapid lysis	1-3	1	1	None
6	1 275	10	3 425	Prompt recovery by crisis	2-3	1	1	None
2	550	6	2 750	Prompt recovery by crisis	3	6	1	None
1	75	5	2 700	Prompt recovery by crisis	3-4	13?	1	Ac alcoholic psychosis

or two earlier as tests were omitted on some days

between 24 and 48 hours after onset

TREATMENTS				RESULT				
Maintenance refills		Total		Clinical course following treatment	Calendar day	Agglutinins first appeared day	Spread to other lobes	Complications
Number of treat ments	Amount of air	Number of treat ments	Amount of air					
	cc		cc					
1	150	6	2 450	Much improved recovery by lysis	4-7	10	—	None
1	500	3	1 600	Improved short relapse recovered by crisis	5	—	—	None
3	625	8	2 775	Markedly improved recovered by crisis	5	10?	—	None
2	400	6	2 900	Markedly improved recovered by lysis	3-5	7?	—	Sterile pleural ef fusion
0	0	3	2 850	Prompt recovery by rapid lysis	2-4		—	None
7	1 600	10	3 625	Much improved recovered by lysis	4-6	9	—	Sterile pleural ef fusion
1	125	(1 tr)	?	Not improved recovered by lysis	6-7	6	—	None
		5	1 200					
2	200	6	2 150	Not improved recovered by crisis	8	8	—	None
0	0	3	1 000	Not improved recovered by crisis	8	7	—	None

pneumothorax

cases treated with small amounts of air and only partial collapse of the involved lung, showed agglutinins in the blood as early as the fifth

third and sixth days, respectively, so that early recovery may have been the natural crisis rather than related to the pneumothorax treatment. Two cases showed transient improvement but relapsed. In the first of these, case R C, an initial treatment of 2220 cc, administered very slowly over a period of 14 hours with the patient lying on his back and sleeping in naps, raised the mean intrapleural pressure to +1.5 cm with the subject in the supine position, probably to the neighborhood of -3 cm in the lateral position. X-ray of the chest following the treatment showed incomplete collapse. Relapse presumably occurred because of inadequate initial treatments and delayed refills, the mean intrapleural pressure at the beginning of the third treatment with the patient lying on the uninvolved side being -6 cm. The other patient, case G S, who was extremely toxic and had fairly advanced consolidation of the left lower lobe, relapsed with a spread to the right upper lobe. None of the 6 cases developed complications.

Of the 9 cases with preexisting fibrous pleural adhesions, only case M C. showed any apparent benefit from the treatment and in this case, since crisis occurred on the fifth day, the result cannot with confidence be attributed to the pneumothorax treatment. Four cases showed further spread of the pneumonia to another lobe, 2 developed empyema, 1 died with a terminal septicemia.

The individual records of all the cases without adhesions and four illustrative cases with adhesions from Group C are presented on pages 42-43.

*Group D Treated later than 72 hours after onset* Data concerning the 14 advanced cases in this group are summarized in table 6, from which it will be seen that artificial pneumothorax exerted no apparent effect on the duration or outcome of the disease in these advanced cases, most of whom were severely ill. In fact even temporary improvement was observed in only one patient, case F R. Eight showed further extension of the pneumonia, 9 died, 2 with complicating empyema. In none of the 6 cases with bacteremia did the treatment exert any apparent influence on the blood stream infection.

The individual records of three illustrative cases from Group D are presented on pages 42-43.

### Discussion

In the foregoing observations on the therapeutic effects of artificial pneumothorax in 42 cases of lobar pneumonia emphasis has been placed on the method of treatment evolved during the course of the study and on the effect of artificial pneumothorax on the clinical course and outcome of the disease in an effort to define tentatively the conditions under which artificial pneumothorax would appear to be therapeutically useful. The results obtained, which are summarized in figure 16, seem to indicate that the procedure is of definite therapeutic value but only under certain limited conditions, namely, (a) when

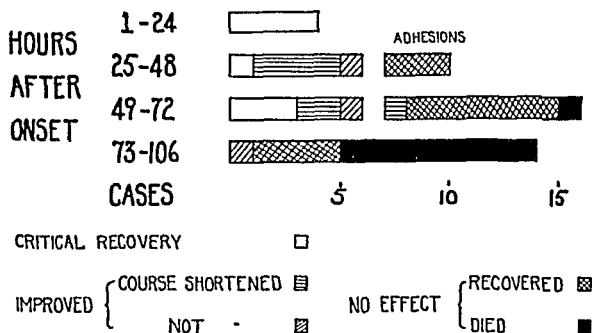


FIG 16 EFFECT OF ARTIFICIAL PNEUMOTHORAX ON THE CLINICAL COURSE OF 42 CASES OF LOBAR PNEUMONIA

the volume of air introduced into the pleural cavity is sufficient to raise the mean intrapleural pressure promptly to +1 to +2 cm with the patient in the lateral position, pneumonic side up, resulting in complete collapse and immobilization of the lung on the affected side, (b) when the frequency and volume of refills is sufficient to maintain the mean pressure at this level and the lung retracted until danger of relapse is past, (c) when treatment is instituted *early* in the disease, i.e., certainly within less than 72 hours after onset, probably within less than 48 hours in most cases, (d) when the pleura is free from adhesions which interfere with retraction of the involved lung

## Cases in which treatment was

## CLINICAL DATA

## PNEUMOTHORAX

Case	Sex	Age	Pneumo- coccus type	Blood cul- tures	Site	Pleural adhe- sions	Begun		Initial series		
							Hours after onset	Calen- dar day	Num- ber of treat- ments	Amount of air	Rise in intraple- press <sup>†</sup>
R C	M	18	VII	—	LL	—	52	3	1	cc	cm
A C	M	25	I	—	RL	—	54	3	2	2,220	-8 to +
T I	M	47	XXVIII	—	RL	—	56	3	4	650	-6 to -
R D	M	44	V	—	RU	—	60	3	2	2,300	-19 to -
J F	M	17	VIII	—	LL	—	61	3	2	750	-7 to -
G S	F	20	I	—	LL	—	64	4	2	650	-8 to -
										2,100	-5 5 to
Ho T	M	47	?	—	RL	++	50	3	1	550	-4 to +
M C	F	28	I	—	RU	++	50	3	4	1,675	-3 to +
F M	M	34	I	—+	LL	++	51	3	2	2,800	-7 5 to
J H	M	32	I	—	RU	++	52	3	2	1,550	-6 to 0
H McV	M	47	VII	—	RL	++	53	3	2	2,800	-4 5 to
D G	M	37	I	+—	LL	++	54	3	2	550	-9 to -
B G	M	30	I	—	RL	++	64	4	3	2,300	-5 to +
W S	M	13	II	—	LL	++	66	4	2	800	-6 to -
R P	M	29	VII	—+	RL	++	67	4	2	1,850	-4 5 to

\* In prone position, collapse incomplete † Air removed from pleural cavity ‡ Right side

## Cases treated by

## CLINICAL DATA

## PNEUMOTHORAX

Case	Sex	Age	Pneumo- coccus type	Blood cul- tures	Site	Pleural adhe- sions	Begun		Initial series		
							Hours after onset	Calen- dar day	Num- ber of treat- ments	Amount of air	Rise in intraple- press <sup>†</sup>
I R	F	35	V	—	RU	—	78	4	2	cc	cm
										600	-8 to -
M S	M	54	V	—	RM	++	80	4	4	2,400	-4 to -
J Sy	M	44	I	—	RU	++	80	4	3	2,150	-5 to -
R Co	M	19	I	—	RL	++	80+	4	3	2,510	-4 5 to
E K	F	40	I	—	LU	++	80+	4	4	1,400	-5 5 to
S C	F	36	V	—	RL	++	82	4	4	2,050	-7 to -
J G	M	41	I	+	RU ML	+	84	4	1	350	-4 to -
A W	F	50	IV	—	LU	+	85	4	3	1,050	-3 to -
A N*	F	30 <sup>‡</sup>	I	+	LU	+	85±?	4±?	3	1,050	-4 to +
R Pa*	M	57	I	+	RU	—	85±?	4±?	4	2,200	-4 5 to
H S	M	27	I	—	LL	++	89	4	3	2,300	-8 5 to
S M	F	48	IV	+	RL	—	90±?	4±?	5	2,000	-3 to +
J L	M	77	VIII	+	LL	+	90	5	3	675	-3 to +
H M	M	58	XVIII	+	RU ML	+	106	5	1	300	Not deter

\* Also treated with Type I serum † Air withdrawn

18 and 72 hours after onset

			RESULT				
Amount of air	Total		Clinical course following treatment	Calendar day	Agglutinins first appeared day	Spread to other lobes	Complications
	Number of treatments	Amount of air					
cc		cc					
1 000	4	3 220	Prompt improvement, relapse recovered by lysis	6-7	9	—	None
400	3	1 050	Prompt recovery by crisis	4	5?	—	None
1 000	6	3 300	Prompt recovery by crisis	3-4	—	—	None
0	2	750	Prompt recovery by crisis	4	3	—	None
300	3	950	Prompt recovery by crisis	4-5	6	—	None
300	3	2 400	Temporary improvement relapse Type I serum on 6th day recovered by crisis	6	—	R U	None
0	1	550	Not improved recovered by lysis	6-9	—	—	None
400	5	2 075	Short, recovered by crisis	5	—	—	None
-1 525	2	2 800	Progressively worse died	8	—	R L	None
	-2	-1 525					
300	3	1 850	Not improved recovered by crisis	6	9?	—	None
500	4	3 300	Not improved recovered by lysis	9-11	10	R U	None
0	2	550	Not improved Type I serum 6th and 7th days		7	—	Empyema
			Recovered				
-850	3	2 300	Not improved recovered		8	—	Empyema
	-2	-850					
285	3	1 085	Not improved recovered by crisis	8	9	R U	None
0	2	1 850	Not improved recovered by lysis	7-9	18?	R U?	None

18 and 72 hours after onset

			RESULT				
Amount of air	Total		Clinical course following treatment	Calendar day	Agglutinins first appeared day	Spread to other lobes	Complications
	Number of treatments	Amount of air					
cc		cc					
0	2	600	Prompt improvement relapse Recovered by crisis	7	9	—	None
700	6	3 100	Not improved recovered by crisis	8-9	8	R U	None
750	6	2 900	Not improved recovered by crisis	7-8	9	—	None
-500	3	2 510	Progressively worse died	7	—	L L	None
	-1	-500					
-150	4	1 400	Not improved died	25	—	R M	Empyema
	-2	-150					
250	5	2 300	Not improved, recovered by crisis	7	9?	—	None
0	1	350	Very severe died	5	—	—	None
0	3	1 050	No improvement died	6	—	—	None
0	3	1 050	No improvement died	10	7	R L	None
-1 000	4	2 200	No improvement died	8	—	L L	Empyema
	-3	-1 000					
0	3	2 300	Not improved recovered by crisis	6-7	—	—	None
0	5	2 000	No improvement, died	6	—	L L	None
0	3	675	No improvement, died	6	—	R M	None
0	1	300	Moribund died	6	—	L U	None



Despite the excellent results obtained in the early cases without interfering adhesions, it nevertheless must be obvious that the foregoing statement concerning the conditions under which artificial pneumothorax treatment would appear to be therapeutically useful can be only a tentative one at present, since the series includes only 10 cases without interfering pleural adhesions in whom treatment was started prior to 48 hours after onset. On the other hand the results obtained would seem to indicate quite clearly that artificial pneumothorax is of little or no therapeutic value in advanced cases of more than 72 hours duration and in even earlier cases with extensive pleural adhesions. In the intermediate group first treated between 48 and 72 hours after onset, the results remain of doubtful significance in view of the early appearance of agglutinins in 3 of the 6 cases without adhesions, and the occurrence of relapse after initial improvement in 2 of the remaining 3.

#### CONCLUSION

One fact would appear to stand out clearly, namely, that artificial pneumothorax is an emergency therapeutic procedure and should be carried out without delay early in the disease if a really beneficial therapeutic effect on the course and outcome of lobar pneumonia is to be obtained, preferably during the first 24 hours after onset, hopefully during the next 24 hours, still hopefully but without too great expectations during the next 24 hours, after not at all unless it be with a small amount of air merely for the relief of pleural pain. No statistical analysis of the results obtained is warranted nor is there sufficient evidence as yet to justify any other conclusion than to quote again what Lieutenant Rood said sixteen years ago: "The use of this operation as a therapeutic measure in selected cases is worthy of further trial."

#### ADDENDUM

During and subsequent to the preparation of this article a considerable number of additional reports on the use of artificial pneumothorax in lobar pneumonia have appeared. Using essentially the procedure followed by Friedemann, Coghlan and others, Liverani (51) treated 6 cases without notable benefit in 5 and concluded that the method

was not useful, Vincenzo (52) treated 5 cases with inconclusive results, Crowell (53), 5 cases, 4 of whom were children, Isaacs, Udesky and DePinto (54), 7 cases with no benefit in 4, Shipman and Cox (55), 22 cases with symptomatic relief in many but without apparent effect on the duration of the disease, and Burbank and Rothstein (56), 20 cases, also with symptomatic relief in many but early crisis in only 2. In fully half of these 65 cases treatment with artificial pneumothorax was not instituted until the fourth day of the disease or later and two-thirds received only one or two treatments usually of 300 to 500 cc. The intervals between treatments varied from 12 to 48 hours except in the cases reported by Burbank and Rothstein (56), who gave a second treatment four to six hours after the first. No clear distinction between cases without and those with pleural adhesions is presented in any of the foregoing reports. Only Shipman and Cox (55) record bacteriological observations on the type of infection and the presence or absence of bacteremia. Because of these facts and in view of our own experience it would appear that at best only symptomatic relief could have been obtained in some, though by no means all of these cases. Analysis of the recorded results would seem to support this assumption.

Stoll, Hopkins and Martin (57) have reported in detail the results obtained in 25 carefully studied cases, in all but 7 of which treatment was instituted prior to the fourth day. Beginning at first with small amounts of air given at intervals of approximately twelve hours, they subsequently gave the first three or four treatments at intervals of four to six hours with a follow-up refill after the temperature had fallen to normal. The frequent presence of pleural adhesions was found to be the greatest obstacle to successful treatment. As a result of their experience they conclude that pain is relieved and a prompt lessening of the toxemia may be expected when compression can be effected early and maintained and that artificial pneumothorax is probably the best type of treatment for the types of infection for which there is no anti-serum available.

Bullowa (58), on the other hand, who has reported on the results obtained in 40 carefully studied cases of pneumococcal lobar pneumonia, in 35 of which treatment was initiated prior to the fourth day of the disease, and Bullowa and Mayer (59) have not been favorably

impressed with the effect of artificial pneumothorax therapy and believe that the hazards of the procedure outweigh its alleged advantages. In support of this view they cite the following complications and disadvantages which they have noted,—late invasion of the blood by pneumococci, homolateral extension of the infection, contralateral spread of the pneumonia, empyema, induced rupture of the lung, extreme mediastinal shift with death, harmful delay in serum therapy, and fatigue of patients by frequent manipulation and roentgen examinations. The first four would appear to be hazards of the disease rather than of the therapy, the next two of extremely rare occurrence, the last adequately counterbalanced by relief of pleural pain, restlessness and insomnia. As pointed out by Leopold and Lieberman (60) there is no obvious reason why pneumothorax treatment should be a bar to the simultaneous use of other methods of therapy or cause delay in the use of serum in those types of infection for which serum is available. Of the 35 cases treated by Bullowa (58) before the fourth day, 3 died. Of these one received only one treatment, at least one had adhesions and died with a complicating hemolytic streptococcal infection and one developed a contralateral spread and empyema. Twelve recovered prior to the seventh day. Four of these also received antipneumococcal serum. In spite of Bullowa's unfavorable report we believe from our own experience (61) that further trial of artificial pneumothorax in lobar pneumonia is desirable and should be carried out under carefully controlled conditions.

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## CASE RECORDS

Records of 26 of the 42 cases of lobar pneumonia treated with artificial pneumothorax are presented in the following pages. The charts show at the top the hospital number, case initials, sex, age, pneumococcus type and lobes involved. Day is calendar day of the disease,  $x_1^x$ ,  $x_2^x$ , etc., indicate roentgenograms, the numbers corresponding with the numbers on the x-ray pictures, vertical lines indicate pneumothorax treatments, the volume of air introduced at each treatment being shown by the length of the line, temperatures are rectal, intrapleural pressures are recorded at the beginning and end of each treatment in centimeters of water, *AGGL* = serum agglutinins, *BC* = blood culture, *WBC* = total leukocyte count, *S* = Type I serum treatment, *Th* = thoracentesis.

N0 A53669 R.A ♂ 20 TYPE V LLL

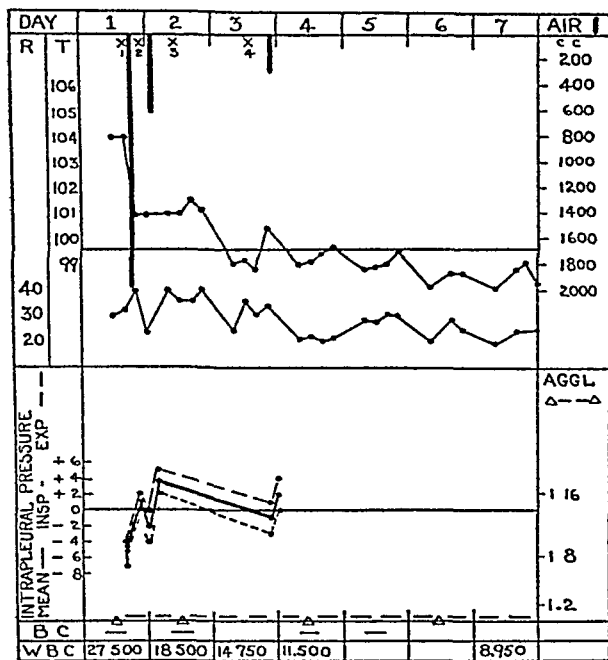


FIG 17A CASE R A

*Mar 19, 1935.* 10 00 a m Onset with chill followed by pain in left lower chest  
3 00 p m, admitted Impaired resonance and diminished breath sounds over left  
lower lobe 4 00 p m X-ray 1, pneumonia, left lower lobe, preconsolidative stage  
6 45-8 28 p m First pneumothorax treatment, 6 hrs after onset, patient on right  
side, 2000 cc of air introduced without difficulty, average rate 19 4 cc per min, mean  
intrapleural pressure raised from -4 5 to +1 cm Transient pain in left chest with  
change of position suggesting adhesion 10 00 p m X-ray 2, partial collapse, apical  
adhesion  
*Mar 20* 2 00-2 35 a m Second pneumothorax treatment, 600 cc, average rate 17 1 cc  
per min, mean intrapleural pressure raised from -2 to +3 5 cm 10 00 a m Much  
improved X-ray 3, complete collapse of left lower lobe, apex of left upper lobe  
held out by adhesion  
*Mar 21* Comfortable 2 00 p m X-ray 4, and special x-ray studies (cf fig 10)  
10 02-10 11 p m Maintenance refill, 300 cc, average rate 33 3 cc per min  
*Mar 22* Appears well  
*Mar 29* X-ray 5, left upper lobe expanding  
*Mar 30* Convalescence uneventful Discharged.  
*May 1* Follow up x-ray 6  
*Comment* Early case, adequately treated, prompt relief of symptoms, early recovery  
without development of agglutinins

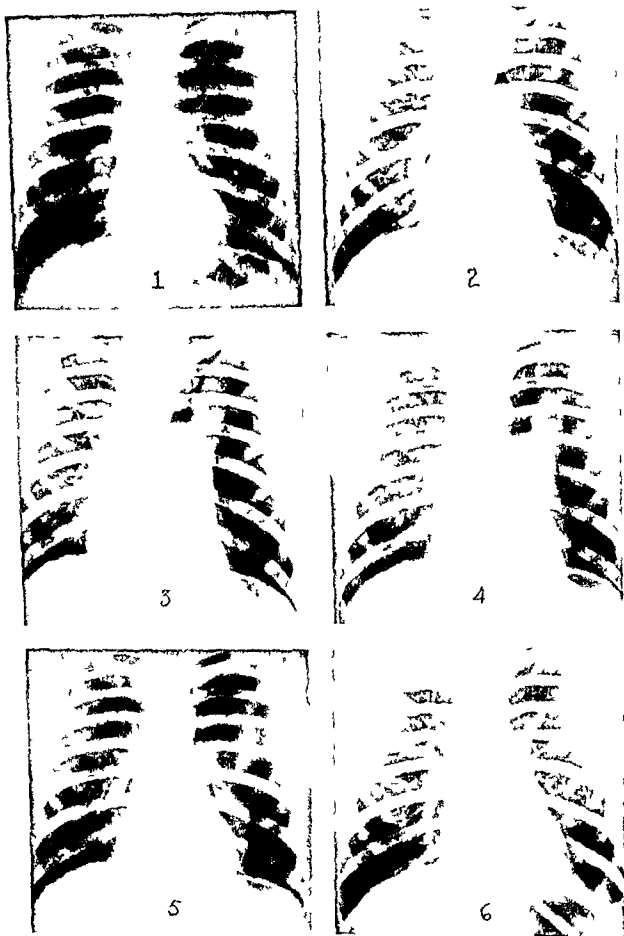


FIG 17B. CASE R. A. SERIAL ROENTGENOGRAMS

1, pre treatment, 2, partial collapse following 2000 cc of air, 3 complete collapse after 2600 cc of air, apical adhesion, 4 collapse maintained, 5, beginning re expansion, 6, air completely absorbed



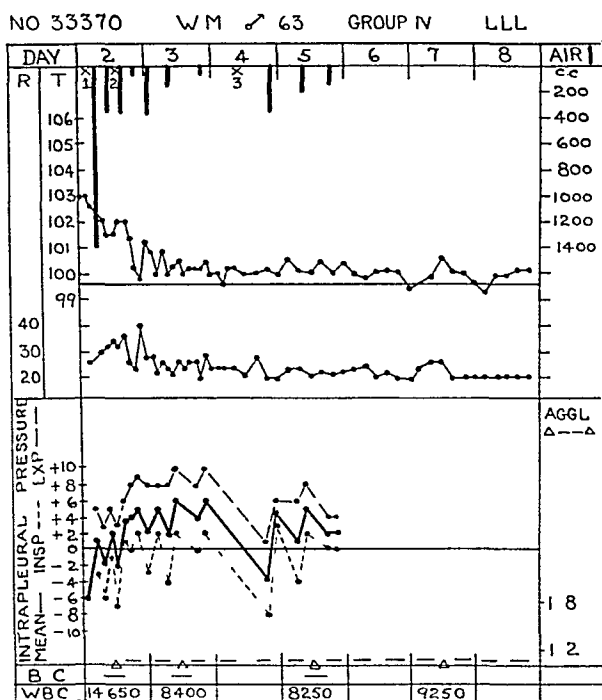


FIG 18A CASE W M

Mar 11 1934 9 00 p.m. Onset with sudden severe pain in anterior left lower chest, rapidly becoming worse and associated with malaise and fever

Mar 12 3 15 a.m., admitted. Bloody sputum, slight cyanosis, left chest splinted, at the left base, from the angle of the scapula down and extending into the axilla, dullness, slight increase in fremitus, suppression of breath sounds and numerous crepitant rales, loud friction rub in the axilla. 3 30 a.m. X-ray 1. Pneumonia, left lower lobe, preconsolidative stage. 6 15 to 6 58 a.m., first pneumothorax treatment, 9 hrs after onset patient on right side, 1400 cc, average rate 32.6 cc per min, changing the mean intrapleural pressure from -5.5 to +1.0 cm. 8 00 a.m., pain gone and patient comfortable. 10 19 to 10 35 a.m., second air injection, 350 cc, average rate 21.9 cc per min, mean intrapleural pressure raised from -1.5 to +2.0 cm. 2 00 p.m. X-ray 2, almost complete collapse. 2 50 to 3 06 p.m. third air injection 350 cc, rate 21.9 cc per min, mean intrapleural pressure raised from -2 to +3.5 cm. 8 00 p.m. 4th air injection 50 cc, pressure readings +4 to +5.5 cm.

Mar 13 Appears well. Three maintenance refills of 375, 150 and 50 cc, respectively, kept the mean pressure elevated to +6 cm.

Mar 14 X-ray 3 complete collapse, subsequent air injections of 350, 200 and 150 cc were given to maintain the positive intrapleural pressure.

Mar 26 Convalescence uneventful. X-ray 4. Discharged.

Comment Early case, adequately treated, prompt relief of symptoms, early recovery without development of agglutinins.

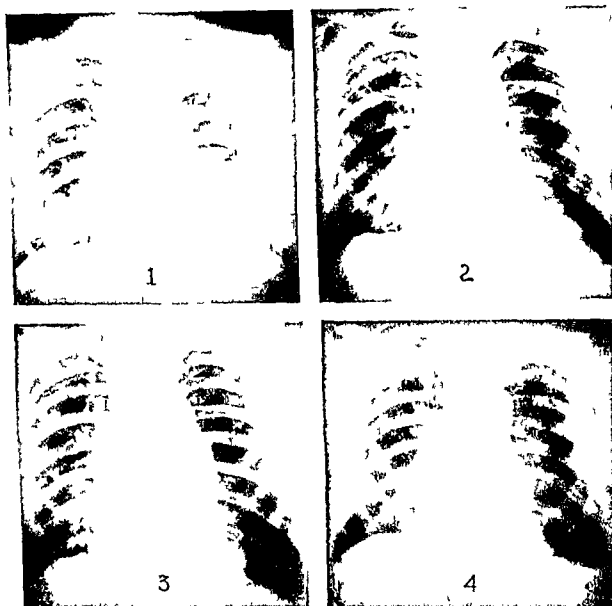


FIG 18B CASE W VI SERIAL ROENTGENOGRAMS

1, early left lower lobe pneumonia pre treatment 2, collapse of left lung after 1750 cc of air, 3 collapse maintained by further treatments, 4, beginning expansion of left upper lobe, small pleural effusion



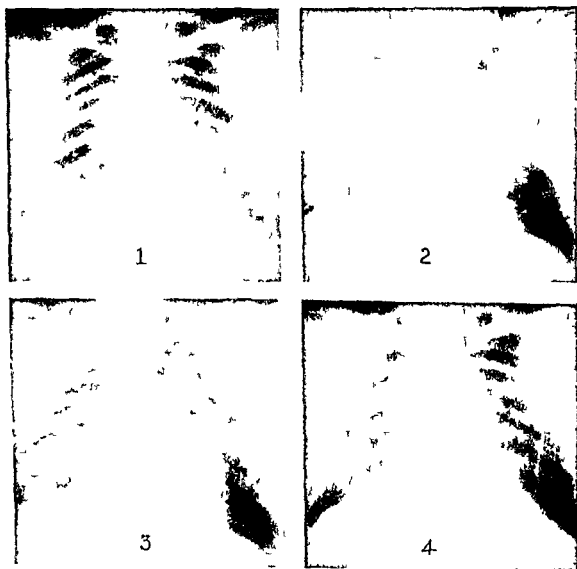


FIG 19B CASE J S SERIAL ROENTGENOGRAMS

1, pre treatment, 2, collapse of left lower lobe after 1800 cc of air, adhesions over left upper lobe, 3 and 4, collapse maintained

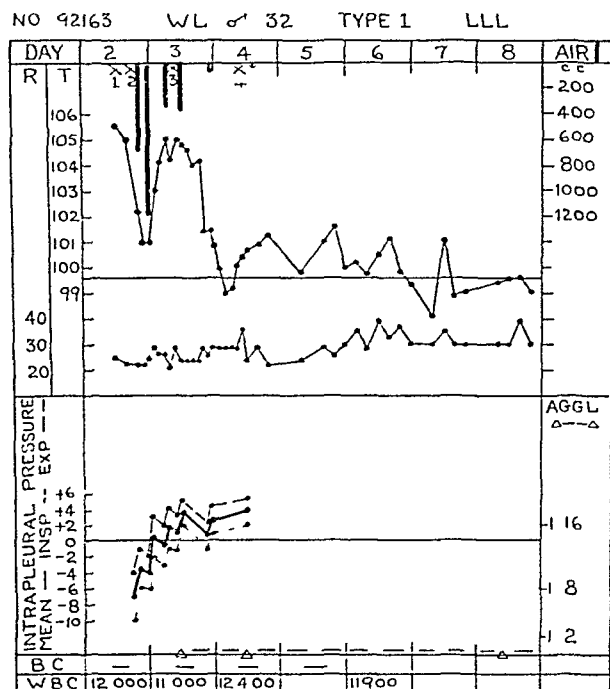


FIG 20A CASE W L

April 15, 1934 Went on severe alcoholic debauch April 17-18, chill during the night  
 April 18 12 00 noon, admitted Appeared toxic, dry cough, soreness deep in left chest, signs of early pneumonia, left lower lobe No friction rub 12 30 p m X-ray 1, question of early pneumonia, left lower lobe 7 00 p m X-ray 2, early pneumonia, left lower lobe 8 00 to 8 18 p m, first pneumothorax treatment, 24 hrs after onset, 700 cc, patient on right side, average rate 38 8 cc per min, change in mean intrapleural pressure from -7 to -3 5 cm

April 19 12 04 to 12 27 a m, second pneumothorax treatment, 1200 cc, average rate 52 2 cc per min, mean pressure raised from -4 to +0 5 cm 7 00 to 7 13 a m, third treatment, 350 cc, rate 27 cc per min, intrapleural pressure raised from -0 5 to +1 5 cm 9 00 a m X-ray 3, showed good though not complete collapse 11 51 a m to 12 07 p m fourth treatment, 375 cc, rate 23 4 cc per min Patient complained of slight respiratory difficulty and choking sensation at the end, the intrapleural pressure having been raised from +1 to +3 5 cm During the evening patient's temperature fell rapidly Intrapleural pressure reading at 10 35 p m, +0 5 cm, rose to +2 5 cm with the injection of 75 cc of air

April 20 9 00 a m, X-ray 4, complete collapse of the left lung Patient looks well, smoking, hungry 11 45 a m, the intrapleural pressure was +3 5 cm No air was given 11 00 p m, developed acute alcoholic psychosis which persisted until May 27, 1934

June 20 Discharged well

June 28 Follow-up X-ray 5

Comment Severe pneumonia in a marked alcoholic, adequately treated early in the disease with prompt recovery by crisis but convalescence prolonged by an acute alcoholic psychosis

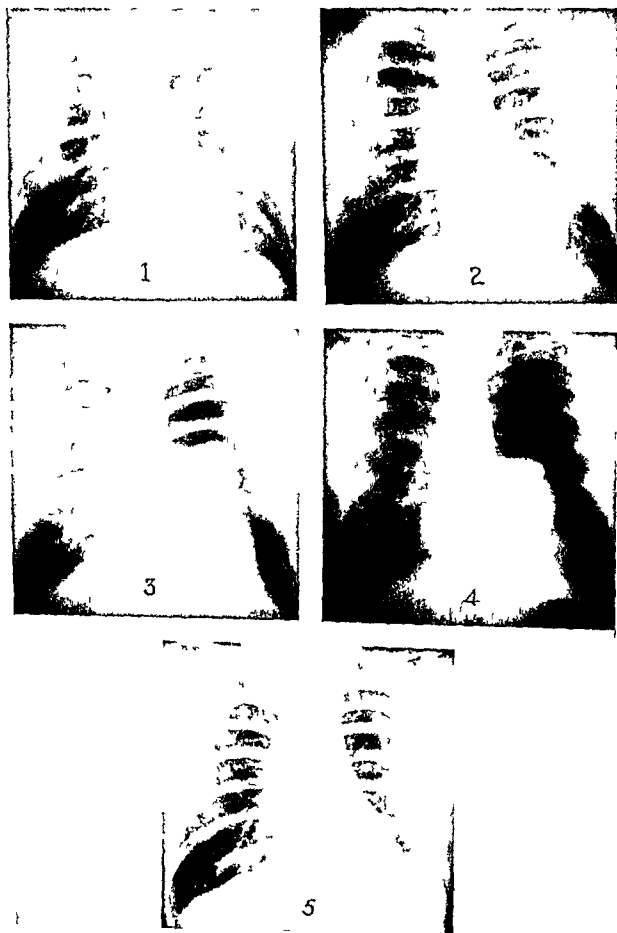


FIG 20B CASL W I SERIAL ROENTGENOGRAMS

1, 16 hrs after onset, interpretation doubtful, 2, 7 hrs later early pneumonia, left lower lobe pre treatment 3 nearly complete collapse after 3 treatments totaling 2250 cc, 4 complete collapse of left lung 5 air absorbed, lung re expanded

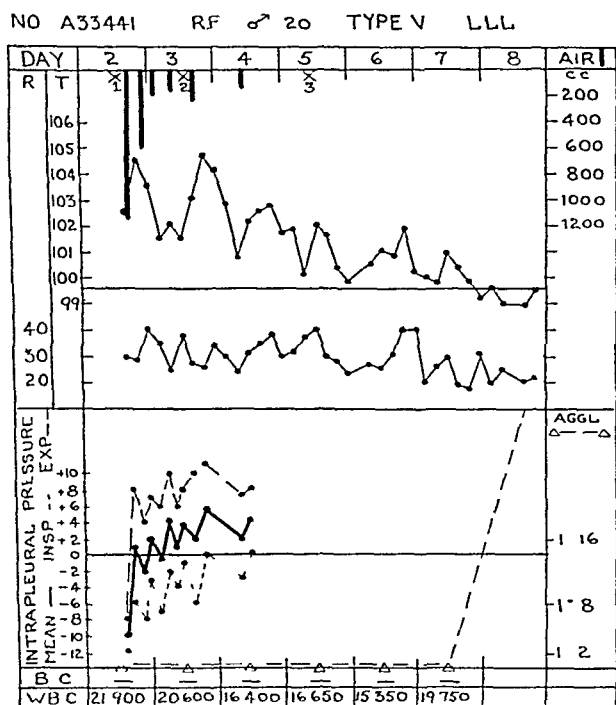


FIG 21A CASE R F

March 17, 1934 4 00 p m Pain left lower chest, anteriorly, followed by short chill, later sweating and fever

March 18 2 35 p m admitted Appeared acutely ill Respirations shallow and accelerated Over the left base behind, extending to the lower mid and anterior axillary regions there is dullness bronchial breathing and occasional rales 4 00 p m X-ray 1 5 18 to 5 48 p m First pneumothorax treatment, 26 hrs after onset, patient on right side, 1125 cc, average rate 37.5 cc per min, with change in mean intrapleural pressure from -10 to +1 cm 10 11 to 10 35 p m Second pneumothorax treatment, 600 cc, rate 25 cc per min, changing intrapleural pressure from -2 to +2 cm Slight pain in left chest on changing position

March 19 2 39 to 2 46 a m Third air injection of 200 cc, bringing mean pressure from -0.5 to +4.0 cm 9 00 a m Improved, pleural pain much relieved 9 09 to 9 15 a m 150 cc of air, which increased the pressure from +1 to +3.5 cm 2 00 p m X-ray 2, practically complete collapse of left lung 4 10 to 4 16 p m, 225 cc of air raised the intrapleural pressure from +2 to +5.5 cm

March 20 Much improved pain gone 10 39 to 10 44 a m, 150 cc of air injected with change in intrapleural pressure from +2 to +4 cm

March 21 X-ray 3 complete collapse

March 30 X-ray 4 upper lobe expanding

March 31 Convalescence uneventful Discharged

May 30 Follow-up x-ray 5

Comment Symptomatically improved, recovery by 14th to 17th days Intrapleural pressure may have been raised higher than necessary by fifth and sixth treatments

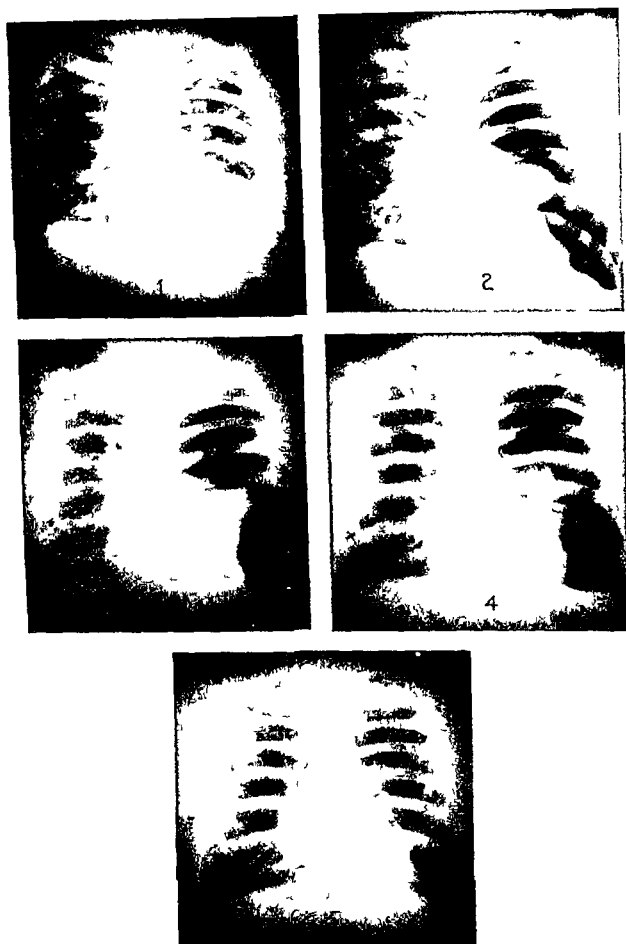


FIG 21B CASE R 17 SERIAL ROENTGENOGRAMS

1 pre treatment, 2 and 3 complete collapse of left lung established and maintained, 4 beginning re expansion of left upper lobe, small pleural effusion, 5 air completely gone, lung fully expanded



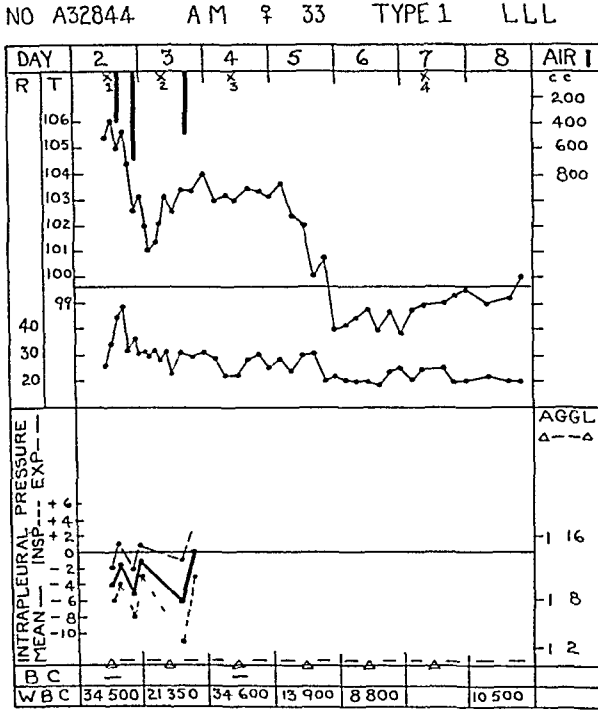


FIG 22a CASE A M

Jan 13, 1934 10 00 a m Sudden severe pain in upper left chest, followed an hour later by chill At noon first raised blood-streaked sputum During afternoon shaking chill and in the evening fever

Jan 14 12 00 noon, admitted Chill, moderate dyspnea and cyanosis Chest expansion limited on left At left base behind, impaired percussion note slightly increased from rhus, distant tubular breathing and crepitant rales 2 30 p m, x-ray 1, pneumonia, left lower lobe, early consolidative stage 4 08 to 4 32 p m, 30 hrs after onset, first pneumothorax treatment, 400 cc, rate 16 6 cc per min, with change in intrapleural pressure from -4 to -1 5 cm 10 30 to 10 52 p m, second treatment, 700 cc of air injected, average rate 31 8 cc per min, changing the mean intrapleural pressure from -5 to -1 cm Slight shortness of breath

Jan 15 Much improved 9 00 a m X-ray 2, partial collapse Relapse 5 04 to 5 17 p m, third air injection, 500 cc, average rate 38 5 cc per min, mean intrapleural pressure changed from -6 to 0 cm

Jan 16 11 45 a m X-ray 3, complete collapse

Jan 17 Marked subjective improvement, critical recovery

Jan 19 X-ray 4

Jan 20 X-ray 5

Discharged Convalescence uneventful

Marked symptomatic improvement following two treatments resulting in collapse of left lung followed by relapse associated with falling intrapleural pressure complete collapse of left lung following third treatment symptomatically probably due to

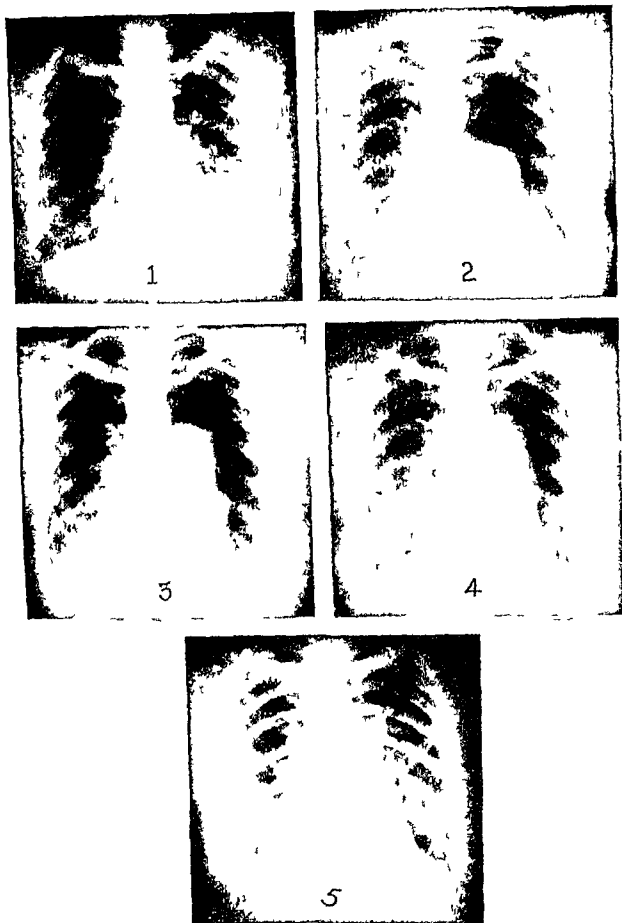


FIG 22B CASL A M SERIAL ROENTGENOGRAMS

1, pre treatment, 2, marked but incomplete collapse of left lung following 2 treatments totalling 1100 cc of air, 3 and 4, complete collapse, small effusion, 5, upper lobe re expanding, small effusion still present

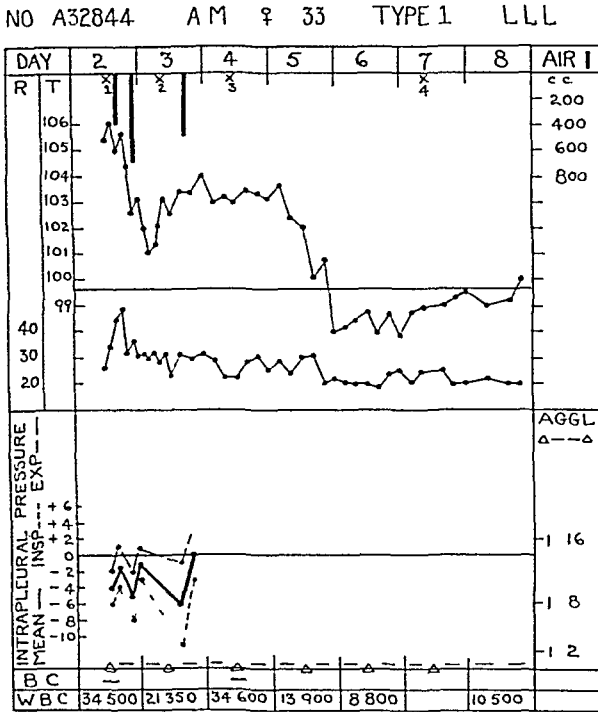


FIG 22A CASE A M

- Jan 13, 1934* 10 00 a m Sudden severe pain in upper left chest, followed an hour later by chill. At noon first raised blood-streaked sputum. During afternoon shaking chill and in the evening fever.
- Jan 14* 12 00 noon, admitted. Chill, moderate dyspnea and cyanosis. Chest expansion limited on left. At left base behind impaired percussion note, slightly increased friction distant tubular breathing and crepitant rales. 2 30 p m, x-ray 1, pneumonia, left lower lobe early consolidative stage. 4 08 to 4 32 p m, 30 hrs after onset first pneumothorax treatment. 400 cc, rate 16.6 cc per min, with change in intrapleural pressure from -4 to -1.5 cm. 10 30 to 10 52 p m, second treatment. 700 cc of air injected average rate 31.8 cc per min, changing the mean intrapleural pressure from -5 to -1 cm. Slight shortness of breath.
- Jan 15* Much improved. 9 00 a m X-ray 2, partial collapse. Relapse. 5 04 to 5 17 p m, third air injection, 500 cc, average rate 38.5 cc per min. mean intrapleural pressure changed from -6 to 0 cm.
- Jan 16* 11 45 a m X-ray 3, complete collapse.
- Jan 17* Marked subjective improvement, critical recovery.
- Jan 19* X-ray 4.
- Jan 26* X-ray 5.
- Jan 27* Discharged. Convalescence uneventful.
- Comment* Marked symptomatic improvement following two treatments resulting in partial collapse of left lung followed by relapse associated with falling intrapleural pressure. Complete collapse of left lung following third treatment, symptomatically improved course probably shortened.

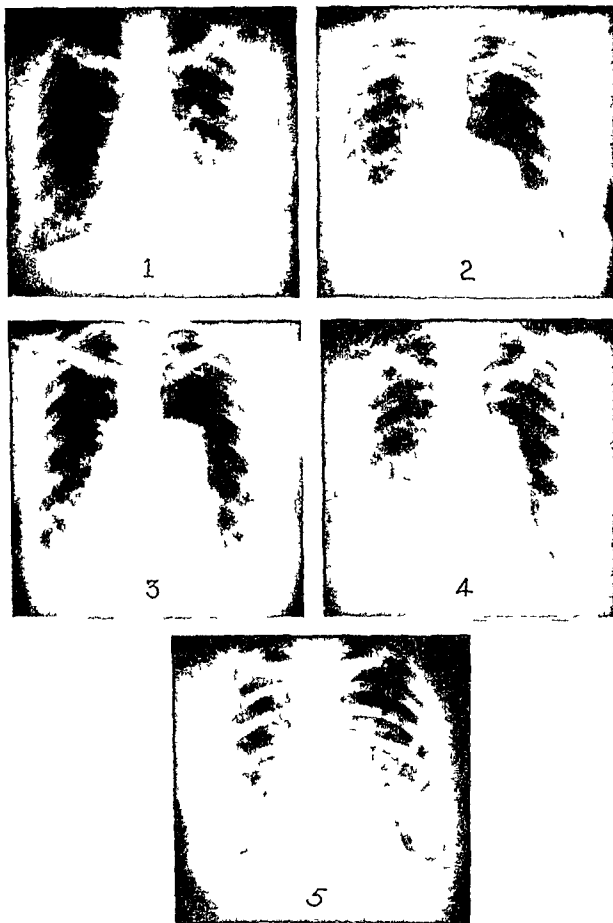
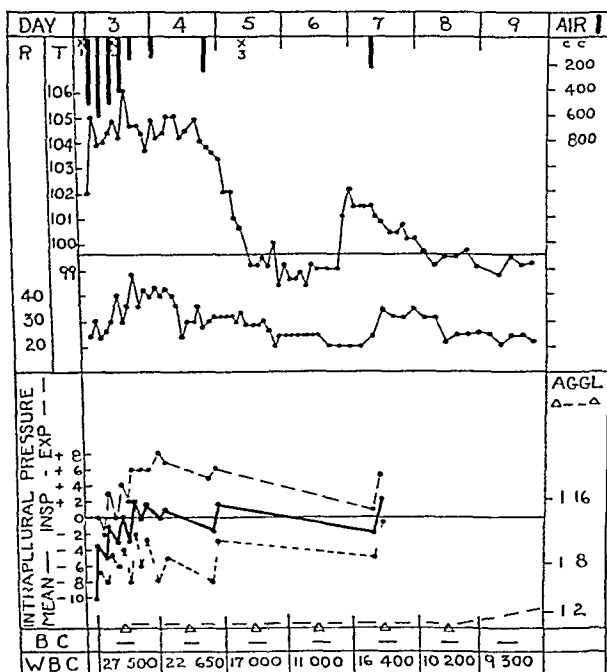


FIG 22B CASE A M SERIAL ROENTGENOGRAMS

1, pre treatment, 2, marked but incomplete collapse of left lung following 2 treatments totalling 1100 cc of air, 3 and 4, complete collapse small effusion 5, upper lobe re expanding, small effusion still present

NO 69096 VG ♀ 30 TYPE 1 RUL



## IIC 23A CASE V G

Feb 22, 1934 5 00 p m Onset with chilly sensations

Feb 23 Feverish, increased cough pain in right axilla on coughing, nausea, headache  
 10 15 p m admitted Moderately toxic and cyanotic Dulness and faint tubular  
 breathing high in right axilla, suppression of breath sounds over right anterior chest  
 11 30 p m X-ray 1, pneumonia, right upper lobe, early

Feb 24 12 07 to 12 19 a m First pneumothorax treatment, 31 hrs after onset,  
 patient on left side, 500 cc average rate 41.7 cc per min, raising mean intrapleural  
 pressure from -10 cm to -3.5 cm Perspired profusely between 2 00 and 3 00 a m  
 4 20 to 4 35 a m second treatment 600 cc, average rate 40 cc per min, pressure  
 changed from -5 to -1 cm Vomited as needle was introduced No other untoward  
 effect 8 47 to 9 02 a m, third pneumothorax treatment, 500 cc, average rate 33.3 cc  
 per min, change in mean pressure from -3 to 0 cm 9 45 a m X-ray 2 Partial  
 collapse 12 15 to 12 33 p m, fourth treatment, 400 cc, average rate 22.2 cc per  
 min with change from -3 to +2 cm in mean pressure Patient dyspnoeic and  
 slightly more cyanotic 4 08 to 4 14 p m, fifth treatment, 150 cc, increasing the  
 pressure from 0 to +1.5 cm Dyspnea now rather marked

Feb 25 12 38 to 12 42 a m sixth treatment 125 cc which brought the pressure again  
 from 0 to +1.0 cm 10 00 a m Symptomatically much improved, no pleural pain,  
 appears less toxic, breathing easily 7 45 to 7 54 p m Seventh treatment, 250 cc,  
 increasing the pressure from -1.5 to +1.5 cm

Feb 26 Crisis fifth day 9 00 a m X-ray 3, greater collapse

Feb 27 Appears well

Feb 28 Temperature elevated 9 20 to 9 26 a m, 250 cc of air injected which brought  
 the pressure from -2 to +2 cm Subsequent fall in temperature

Mar 2 X-ray 4 Complete collapse, slight effusion

Mar 12 X-ray 5 Beginning re-expansion Convalescence uneventful Discharged

Apr 24 Follow-up x-ray 6

Comment Lung rapidly collapsed with frequent small treatments Temporary increase  
 in dyspnea followed by marked symptomatic improvement and early crisis

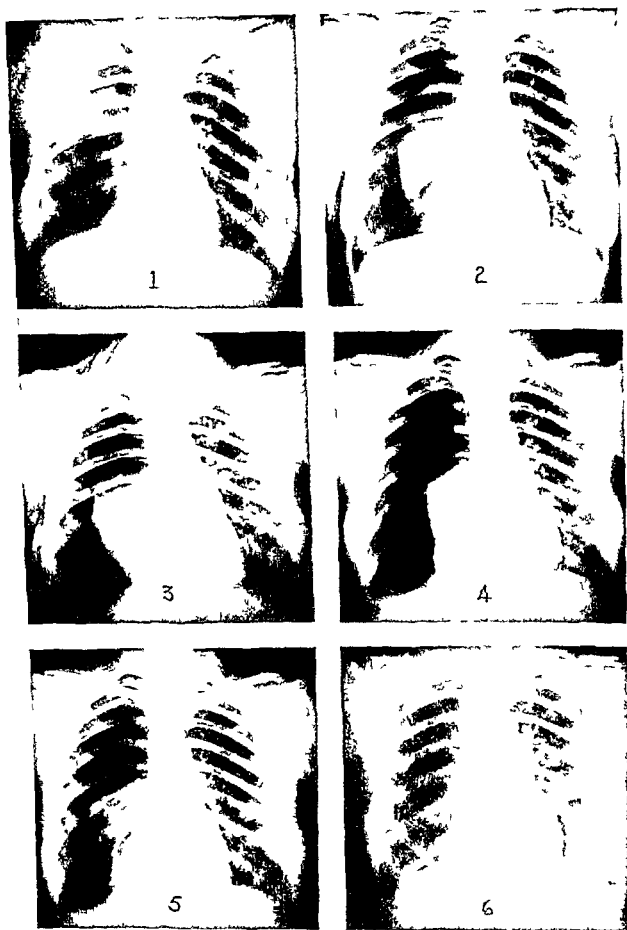


FIG 25B CASE V G SERIAL ROENTGENOGRAMS

1 pre treatment 2, partial collapse after 1600 cc of air 3 and 4, complete collapse established and maintained 5 beginning expansion of right lung 6 air completely absorbed, lung re expanded

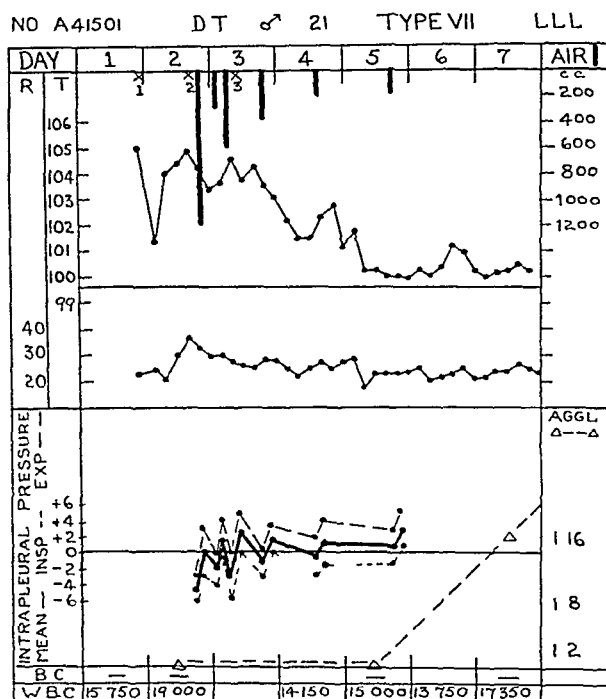


FIG 24\ CASE D T

(Treated through the courtesy of Dr John H Bumstead)

Jan 18, 1935 10 00 a m Onset with pain in mid-chest behind, headache, fever 10 30 p m, admitted, acutely ill, slightly dyspneic Cough productive of purulent and rusty sputum Physical examination and x-ray 1 failed to establish the presence of pneumonia

Jan 19 8 30 a m, respirations increased, slight cyanosis 12 10 p m, pain in left back, definite dullness, distinct bronchial breathing over left base 6 00 p m X-ray 2, well developed pneumonia of left lower lobe 7 00 to 8 45 p m, first pneumothorax treatment, 33 hrs after onset, 1200 cc, average rate 11 4 cc per min with change in mean pressure from -4 5 cm to 0

Jan 20 1 30 to 2 00 a m, second pneumothorax treatment, 300 cc, average rate 10 cc per min, changing the mean pressure from -2 to +1 5 cm Pain in chest relieved when patient is propped up 6 20 to 7 30 a m, third pneumothorax treatment, average rate 10 cc per min, change in intrapleural pressure from -3 to +2 5 cm 9 00 a m X-ray 3 Not quite complete collapse Symptomatically much improved 6 50 to 7 15 p m, fourth treatment, 400 cc, rate 16 cc per min, bringing mean pressure from -1 to +1 5 cm

Jan 21 Improvement continues 2 00 p m, maintenance refill 200 cc

Jan 22 Comfortable, appears well 5 30 p m, refill of 200 cc to maintain a positive intrapleural pressure

Jan 26 2 00 p m X-ray 4, extensive pleural effusion

Jan 30 Thoracentesis, 350 cc of clear yellow, sterile fluid withdrawn Subsequent convalescence uneventful

Feb 14 X-ray 5

Feb 15 Discharged

April 9 Follow-up x-ray 6

Comment Treated by complete collapse of left lung Prompt symptomatic improvement with early recovery by lysis One of the two cases developing a large sterile pleural effusion Earlier treatment presumably would have induced an earlier recovery

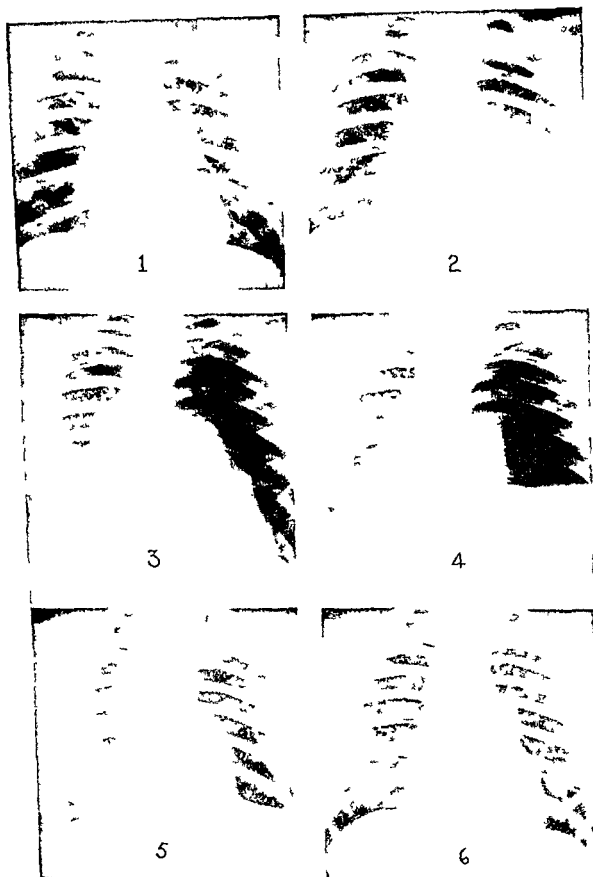


FIG 24B CASE D T SERIAL ROENTGENOGRAMS

1 13 hrs after onset, 2, 19 hrs later, well developed pneumonia of left lower lobe  
 3 collapse after 2100 cc of air, 4, pleural effusion (sterile), 5, lung still collapsed, small  
 effusion remaining, 6, air completely gone, lung re expanded



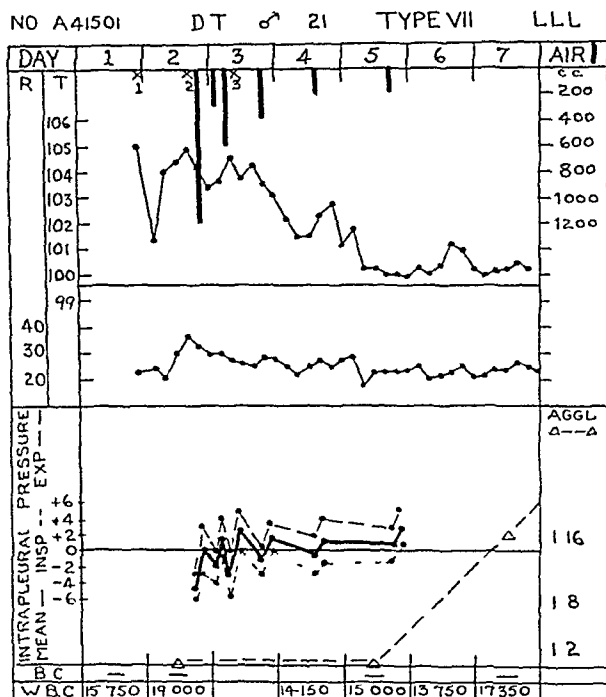


FIG 24A CASE D T

(Treated through the courtesy of Dr John H Bumstead)

Jan 18, 1935 10 00 a m Onset with pain in mid-chest behind  
10 30 p m, admitted, acutely ill, slightly dyspneic Cough pro  
and rusty sputum Physical examination and x-ray 1 failed to c  
of pneumonia

Jan 19 - 8 30 a m, respirations increased, slight cyanosis 12 1  
definite dullness, distant bronchial breathing over left base  
developed pneumonia of left lower lobe 7 00 to 8 45 p m  
ment, 33 hrs after onset, 1200 cc, average rate 11 4 cc  
pressure from -4 5 cm to 0

Jan 20 1 30 to 2 00 a m, second pneumothorax 10 cc per min, changing the mean pressure from relieved when patient is propped up 6 20 to 7 ment, average rate 10 cc per min, change in int 9 00 a m X-ray 3 Not quite complete collapse 6 50 to 7 15 p m fourth treatment, 400 cc sure from -1 to +1.5 cm

Jan 21 Improvement continues 2 00 p

Jan 22	Comfortable, appears well	5
	intrapleural pressure	

Jan 26 2 00 p m X-ray 4, extens-

Jan 30 Thoracentesis, 350 cc of  
convalescence uneventful

1 cb 14 X-ray 5

Feb 15 Discharged

1 April 9 Follow-up x-ray of

**Comment** I reacted by coming  
with early recovery by  
effusion Earlier in

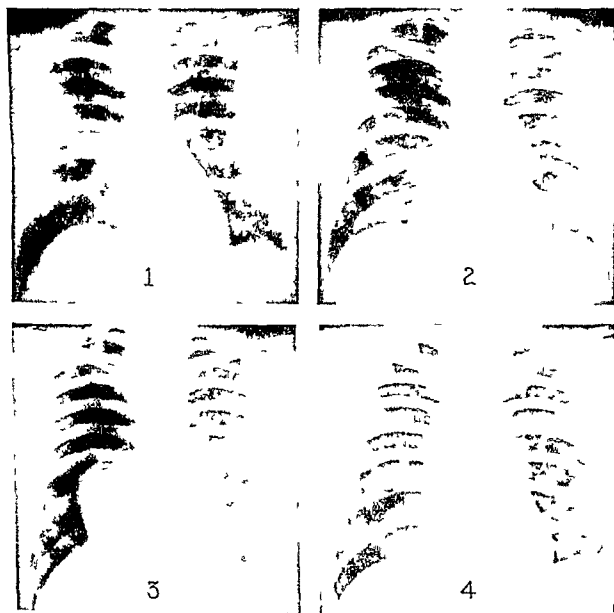


FIG 25B CASE H K SERIAL ROENTGENOGRAMS

1, pre treatment, 2 partial collapse mantle pneumothorax after 1300 cc of air  
3, complete collapse after 2850 cc of air 4, lung re expanding

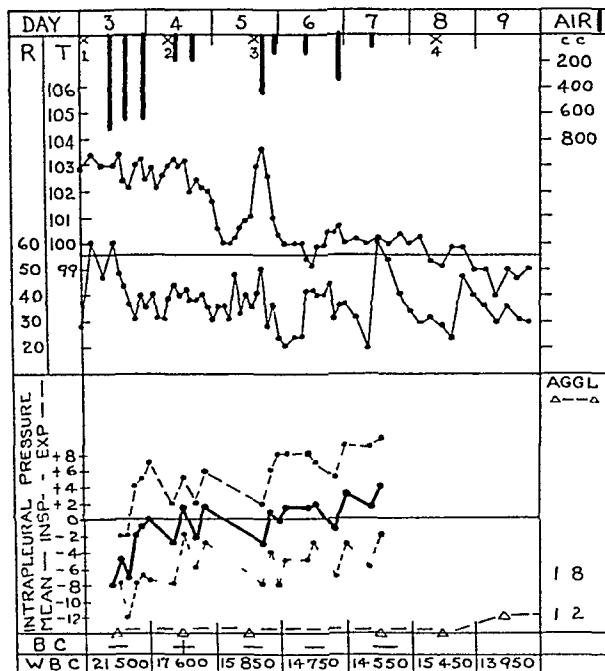


FIG 26A CASE F H ALCOHOLIC RECURRENT RHEUMATIC FEVER SINCE CHILDHOOD  
DYSPNEA ON EXERCISE FOR 9 MONTHS

Mar 5, 1934 9 00 p m Seized with severe pain over right kidney, which moved up under right ribs 9 30 p m Severe chill Began to cough

Mar 6 A m Bloody sputum, high fever, dyspnea, vomited twice 11 30 p m, admitted Grunting, shallow respirations, moderate cyanosis Right chest splnted Dulness, suppressed breath sounds and crepitant rales over right middle and lower lobes Dulness and tubular breathing in the upper axilla and across the midscapular area Heart action rapid but regular Mitral stenosis

Mar 7 12 15 a m X-ray 1, well developed consolidation of all three lobes on right 11 11 to 11 53 a m, first pneumothorax, 38 hrs after onset, patient on left side, 725 cc, rate 17 3 cc per min Initial pressure -8 cm without any fluctuations until 250 cc of air had been given, final mean pressure -5 cm No more air given at this time as patient began to hiccough, became quite cyanotic and pulse at times was quite weak Oxygen tent 5 00 to 5 18 p m, second pneumothorax, 650 cc, rate 36 1 cc per min, raising the mean intrapleural pressure from -7 to -2 cm Oxygen tent 10 50 to 11 13 p m, third pneumothorax, 650 cc of air, rate 28 3 cc per min, bringing the mean intrapleural pressure to 0 from -1 cm Out of Oxygen tent

Mar 8 9 00 a m X-ray 2, good, though incomplete collapse Small air injections at 11 00 a m and 5 00 p m to maintain a positive mean intrapleural pressure, mild dyspnea following the second 11 00 p m, auricular fibrillation Apical rate of 110, radial 90 Digitalized

Mar 9 General condition satisfactory 4 00 p m temperature 103°, question of spread or relapse 4 15 p m X-ray 3, beginning pleural effusion 6 26 to 6 45 p m, sixth pneumothorax, 450 cc, average rate 23 7 cc per min, raising the mean pressure from -3 to +1 cm 11 55 p m small injection of 150 cc Prompt drop in temperature

Mar 10 A m Dyspneic Auricular fibrillation stopped Small air injection to maintain a positive mean intrapleural pressure of +2 to +3 cm

Mar 12 X-ray 4, increase in pleural effusion Convalescence uneventful except for attacks of dyspnea

Mar 26 X-ray 5 effusion larger Discharged

Apr 3 Shortness of breath better

Apr 10 Dyspnea worse X-ray 6, further increase in pleural effusion

Apr 13 Thoracentesis Pressure +2 to -3 cm 400 cc of sterile fluid removed, 200 cc of air injected leaving the mean pressure at -1 cm

Apr 18 X-ray 7, no re-accumulation of fluid

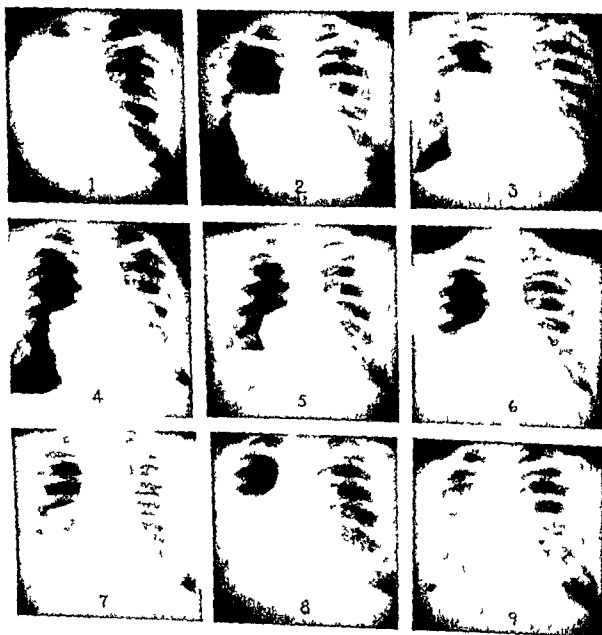


FIG 26B CASE F H SERIAL ROENTGENOGRAMS

1, pre treatment, 2, good though incomplete collapse after 3 treatments totalling 2025 cc, 3, 4, 5, 6 development of large sterile pleural effusion, 7, 8, 9, lung re expanding following thoracentesis

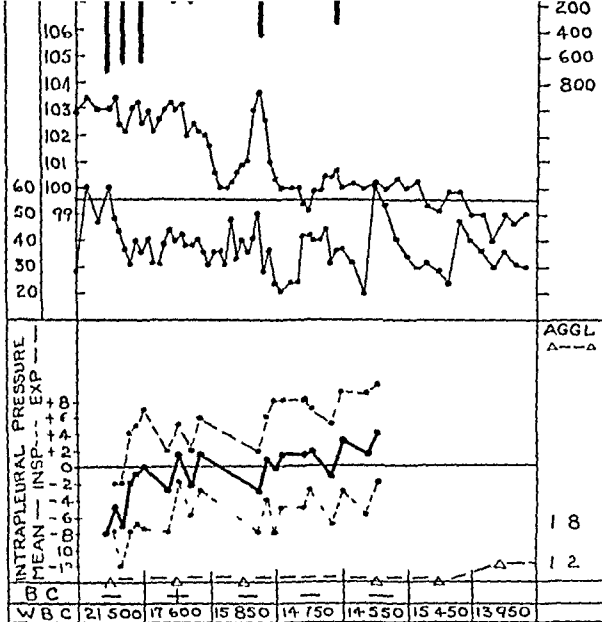


FIG. 26A CASE F H ALCOHOLIC RECURRENT RHEUMATIC FEVER SINCE CHILDHOOD  
DYSPIA ON EXERCISE FOR 9 MONTHS

Mar 5, 1931 9 00 p m Seized with severe pain over right kidney, which moved up under right ribs 9 30 p m Severe chill Began to cough

Mar 6 A m Bloody sputum, high fever, dyspnea, vomited twice 11 30 p m, admitted Grunting, shallow respirations, moderate cyanosis Right chest splinted Dulness, suppressed breath sounds and crepitant rales over right middle and lower lobes Dulness and tubular breathing in the upper axilla and across the midscapular area Heart action rapid but regular Mitral stenosis

Mar 7 12 15 a m X-ray 1, well developed consolidation of all three lobes on right 11 11 to 11 53 a m, first pneumothorax, 38 hrs after onset, patient on left side, 725 cc, rate 17 3 cc per min Initial pressure -8 cm without any fluctuations until 250 cc of air had been given, final mean pressure -5 cm No more air given at this time as patient began to hiccough, became quite cyanotic and pulse at times was quite weak Oxygen tent 5 00 to 5 18 p m, second pneumothorax, 650 cc, rate 36 1 cc per min, raising the mean intrapleural pressure from -7 to -2 cm Oxygen tent 10 50 to 11 13 p m, third pneumothorax, 650 cc of air, rate 28 3 cc per min, bringing the mean intrapleural pressure to 0 from -1 cm Out of Oxygen tent

Mar 8 9 00 a m X-ray 2, good, though incomplete collapse Small air injections at 11 00 a m and 5 00 p m to maintain a positive mean intrapleural pressure, mild dyspnea following the second 11 00 p m, auricular fibrillation Apical rate of 110, radial 90 Digitalized

Mar 9 General condition satisfactory 4 00 p m temperature 103°, question of spread or relapse 1 15 p m X-ray 3, beginning pleural effusion 6 26 to 6 45 p m, sixth pneumothorax 450 cc, average rate 23 7 cc per min, raising the mean pressure from -3 to +1 cm 11 55 p m small injection of 150 cc Prompt drop in temperature

Mar 10 A m Dyspnea Auricular fibrillation stopped Small air injection to maintain a positive mean intrapleural pressure of +2 to +3 cm

Mar 12 X-ray 4 increase in pleural effusion Convalescence uneventful except for attacks of dyspnea

Mar 20 X-ray 5, effusion larger Discharged

Apr 3 Shortness of breath better

Apr 10 Dyspnea worse X-ray 6 further increase in pleural effusion

Apr 13 Thoracentesis Pressure +2 to -3 cm 400 cc of sterile fluid removed, 200 cc. of air injected leaving the mean pressure at -1 cm

Apr 18 X-ray 7 no re-accumulation of fluid

May 9 Some dyspnea and palpitation X-ray 8

June 13 X-ray 9 Returned to work 3 weeks ago

Comment An extremely sick patient with rheumatic heart disease, cardiac dyspnea and transient auricular fibrillation Well developed pneumonia of whole right lung transient bacteremia Auricular pneumothorax treatment followed by surprisingly

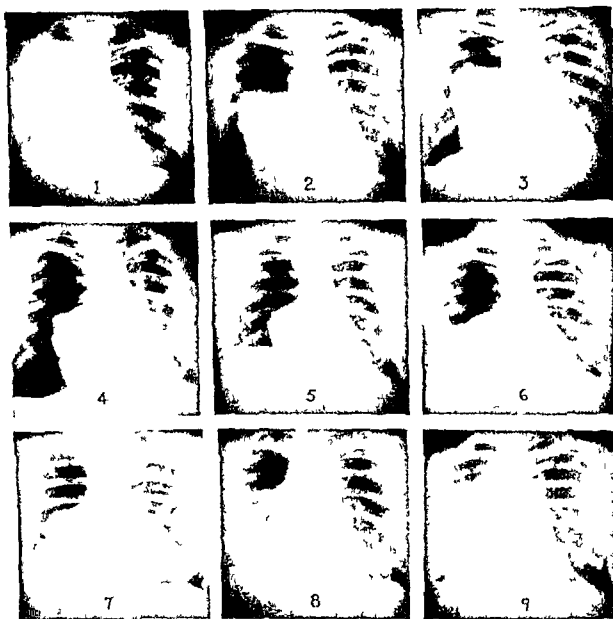


FIG 26B CASE F H SERIAL ROENTGENOGRAMS

1 pre treatment, 2, good though incomplete collapse after 3 treatments totalling 2025 cc, 3, 4 5 6, development of large sterile pleural effusion, 7, 8, 9, lung re expanding following thoracentesis

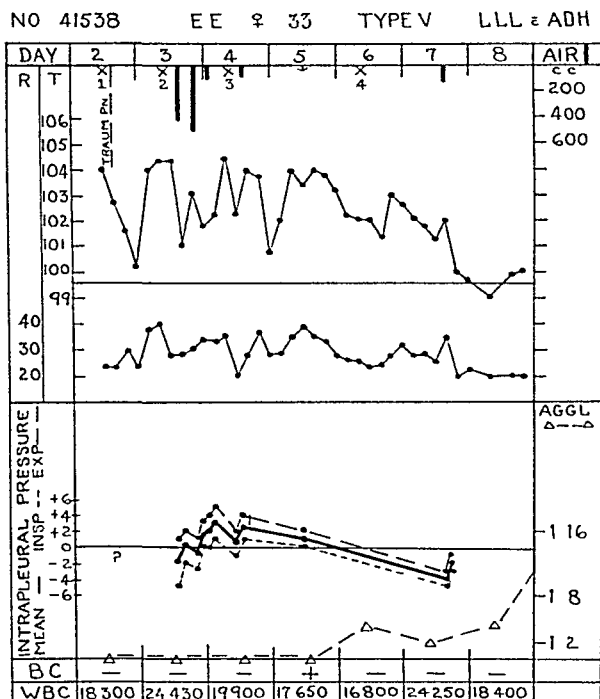


FIG 27A. CASE E E. PLEURISY IN CHILDHOOD

- Oct 10, 1934* 7 30 p m, shaking chill, pain in left lower chest, fever, sputum bloody  
*Oct 11* 12 00 noon, admitted. Acutely ill, face flushed. Respirations rapid and shallow, slight cyanosis. Dulness and crepitant rales at left base behind, where breath and voice sounds were suppressed. 1 00 p m X-rays 1a and 1b, pneumonia of left lower lobe, early stage. 3 10 p m First pneumothorax treatment unsuccessful because of adhesions. 7 00 p m complained of severe pain in left axilla.  
*Oct 12* 9 00 a m More toxic, slightly cyanotic, pleural pain severe, sputum bloody. 10 00 a m X-ray 2, traumatic pneumothorax. 3 24 to 3 54 p m, second pneumothorax treatment with patient on right side, 425 cc, average rate 14.2 cc per min, mean pressure changed from -2 to 0 cm, pleural pain not relieved. 8 19 to 9 08 p m, third treatment, 500 cc, with resulting change in pressure from -1 to +1.5 cm.  
*Oct 13* 1 24 to 1 30 a m Pressure readings, only 75 cc of air injected, intrapleural pressure +2 to +3 cm. 9 15 a m X-ray 3, upper lobe collapsed, lower lobe only partially collapsed due to adhesions, small pleural effusion. 2 00 p m Pressure readings +0.5 to +2.5 cm after the injection of 75 cc of air.  
*Oct 14* No improvement. Blood culture positive. 12 00 noon, mean pressure +1.0 cm.  
*Oct 15* X-ray 4, slight re-expansion, slightly more fluid.  
*Oct 16* 3 24 to 3 33 p m, on right side and flat, 125 cc of air given with a change in pressure from -4 to -2 cm. No longer dyspneic. No cyanosis.  
*Oct 17* Temperature normal. Uneventful convalescence.  
*Oct 27* Discharged.  
*Nov 17* Follow-up X-ray 5.  
*Comment* Failure of artificial pneumothorax to affect course of disease in patient with pleural adhesions preventing complete collapse of involved left lower lobe. Only case in which a traumatic pneumothorax occurred.

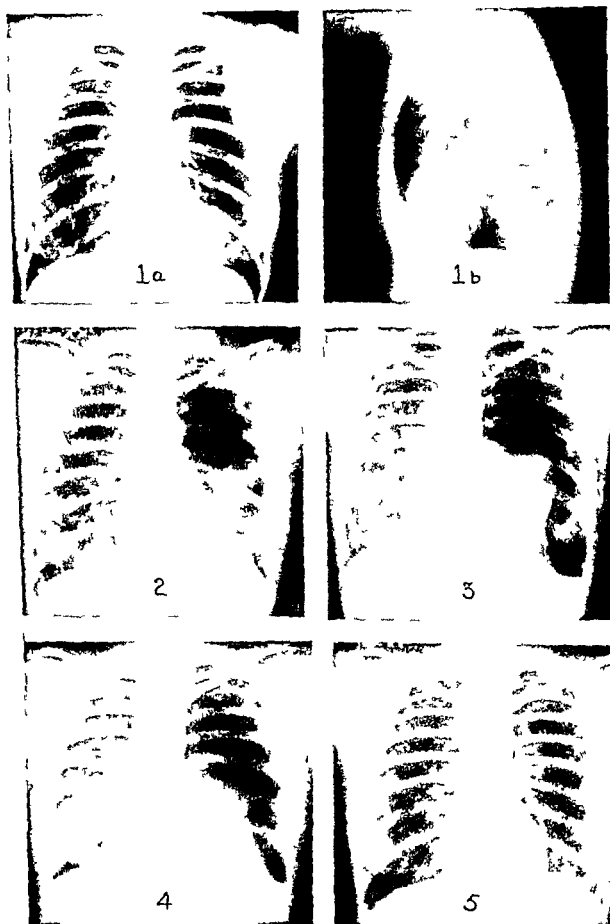


FIG 27B CASE 1 F SERIAL ROENTGENOGRAMS

1a and b pre treatment 2, traumatic pneumothorax 3 upper lobe collapsed, lower lobe only partially, due to adhesions, 4, beginning re expansion, 5, air completely absorbed lung re-expanded



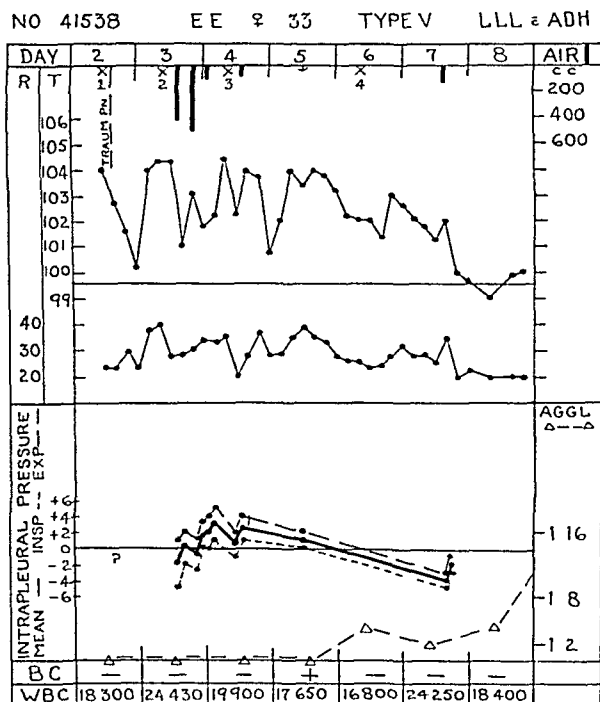


FIG 27A CASE L E PLEURISY IN CHILDHOOD

- Oct 10, 1934 7 30 p m, shaking chill, pain in left lower chest, fever, sputum bloody  
 Oct 11 12 00 noon, admitted Acutely ill, face flushed Respirations rapid and shallow, slight cyanosis Dulness and crepitant rales at left base behind, where breath and voice sounds were suppressed 1 00 p m X-rays 1a and 1b, pneumonia of left lower lobe, early stage 3 10 p m First pneumothorax treatment unsuccessful because of adhesions 7 00 p m complained of severe pain in left axilla  
 Oct 12 9 00 a m More toxic, slightly cyanotic, pleural pain severe, sputum bloody 10 00 a m X-ray 2, traumatic pneumothorax 3 24 to 3 54 p m, second pneumothorax treatment with patient on right side, 425 cc, average rate 14.2 cc per min, mean pressure changed from -2 to 0 cm, pleural pain not relieved 8 19 to 9 08 p m, third treatment, 500 cc, with resulting change in pressure from -1 to +1.5 cm  
 Oct 13 1 24 to 1 30 a m Pressure readings, only 75 cc of air injected, intrapleural pressure +2 to +3 cm 9 15 a m X-ray 3, upper lobe collapsed, lower lobe only partially collapsed due to adhesions, small pleural effusion 2 00 p m Pressure readings +0.5 to +2.5 cm after the injection of 75 cc of air  
 Oct 14 No improvement Blood culture positive 12 00 noon, mean pressure +1.0 cm  
 Oct 15 X-ray 4, slight re-expansion, slightly more fluid  
 Oct 16 3 24 to 3 33 p m, on right side and flat, 125 cc of air given with a change in pressure from -4 to -2 cm No longer dyspneic No cyanosis  
 Oct 17 Temperature normal Uneventful convalescence  
 Oct 27 Discharged  
 Nov. 17 Follow-up X-ray 5  
 Comment Failure of artificial pneumothorax to affect course of disease in patient with pleural adhesions preventing complete collapse of involved left lower lobe Only case in which a traumatic pneumothorax occurred

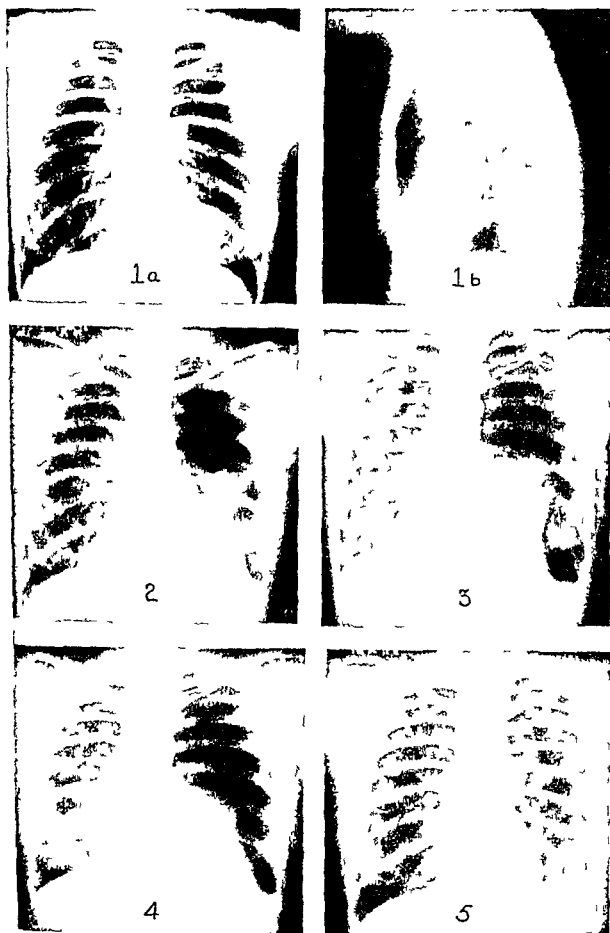


FIG 27B CASE E F SERIAL ROENTGENOGRAMS

1a and b, pre treatment 2, traumatic pneumothorax, 3, upper lobe collapsed, lower lobe only partially, due to adhesions, 4, beginning re expansion, 5, air completely absorbed, lung re expanded

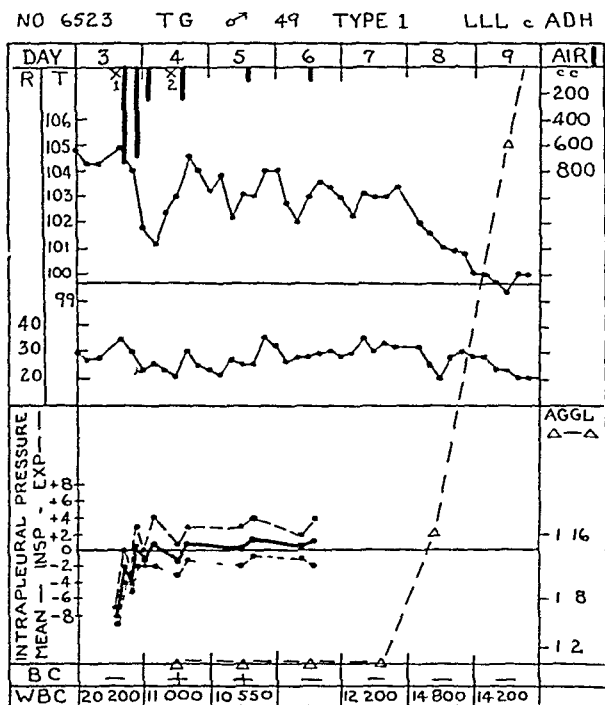


FIG 28A CASE T G PNEUMONIA IN 1918

Dec 20, 1934 9 00 p m Pain in left chest while at work Felt sick, vomited 10 20 p m, admitted on the surgical service Cough productive of grayish-red, flecked sputum Moist rales and variable friction rub just below left nipple Impression, pleurisy

Dec 21 A m No localizing signs of pneumonia

Dec 22 10 00 a m Left side of chest splinted Just below angle of left scapula there is a small area of dullness with increased breath sounds and a few crepitant rales 12 00 noon, signs had increased 3 00 p m X-ray 1, pneumonic infiltration, upper part of the left lower lobe 4 11 to 5 20 p m First pneumothorax, 45 hrs after onset, 750 cc, rate 10 9 cc per min, change in mean intrapleural pressure from -8 to -2 cm Transient, mild, toxic psychosis 8 30 to 9 10 p m, second pneumothorax, 700 cc rate 17 5 cc per min, intrapleural pressure increased from -4 to +0 5 cm Sweated profusely

Dec 23 1 18 to 1 37 a m, third pneumothorax, 250 cc with pressure change from -1 to +1 cm 8 30 a m X-ray 2, partial collapse of upper lobe, lower lobe held out by adhesions Blood culture positive

Dec 23-25 Three small air injections to keep mean intrapleural pressure positive Course of disease unaltered Recovery by crisis

Jan 12, 1935 X-ray 3

Jan 17 Discharged

Comment Failure of artificial pneumothorax to affect course of disease in patient with extensive pleural adhesions

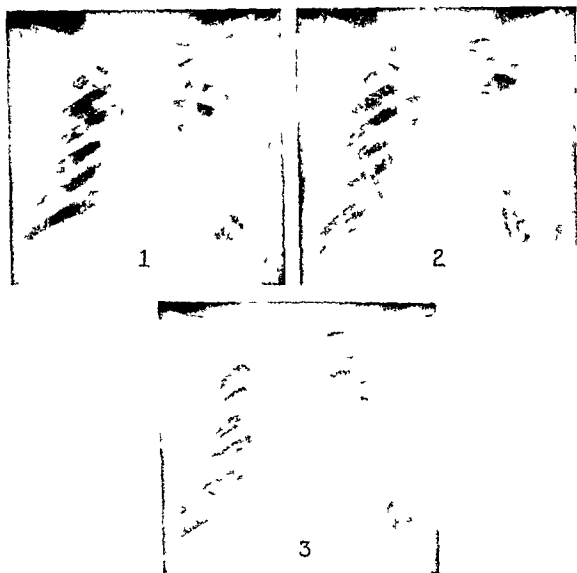


FIG 28B CASE T G SERIAL ROENTGENOGRAMS

1, pre treatment, 2 localized pneumothorax at apex, extensive adhesions, 3, air absorbed lung re expanded

NO 38027 HT 36 TYPE IIATYP RU RLL:ADH

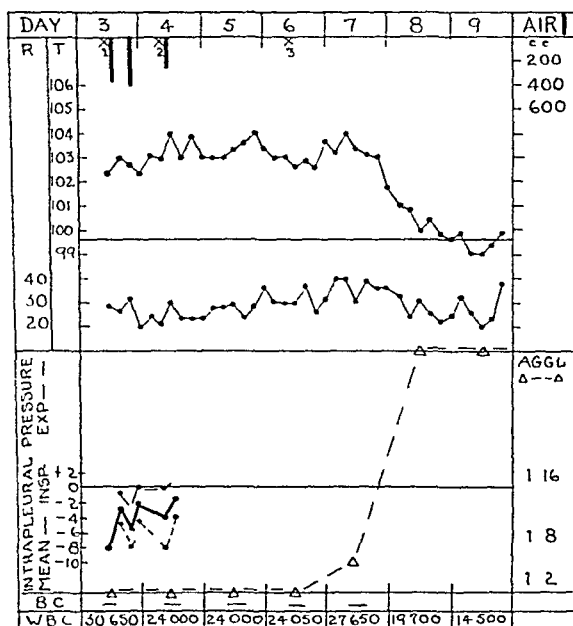


FIG 29A CASE H T

*Jan 30, 1934* During afternoon, chill, malaise, severe pain in right anterior lower chest. Felt feverish, nauseated and found it hard to breathe. Continued work. Worse during night.

*Jan 31* Worse. Pain in epigastrium, nauseated. Continued to work.

*Feb 1* Felt very ill. Admitted 11 00 a.m. Gravely ill. Moderate dyspnea. Slight cyanosis. Examination of chest showed a friction rub over right front at third intercostal space, a few rales and somewhat altered breath sounds high in right axilla, diminished breath sounds and rales in the right paravertebral region over the lower lobe. Dulness in these areas not very marked. 11 30 a.m. X-ray 1, early pneumonia, lower portion of right upper lobe and medial portion of the right lower lobe. 1 24 to 1 39 p.m., first pneumothorax treatment, 46 hrs after onset, patient on left side, 350 cc, average rate 23 cc per min. mean intrapleural pressure changed from -8 to -3 cm. 8 13 to 8 23 p.m., second pneumothorax, 400 cc, average rate 40 cc per min, raising mean pressure from -5.5 to -2.5 cm.

*Feb 2* Chest pain eased though epigastric pain persisted. 8 30 a.m. X-ray 2, partial collapse, upper lobe adherent to chest wall. 10 07 to 10 15 a.m., third pneumothorax, 250 cc with change in mean pressure from -4 to -1.5 cm.

*Feb 3* No change in general condition.

*Feb 4* X-ray 3, consolidation further developed.

*Feb 5* Slight jaundice.

*Feb 8* Crisis during night. X-ray 4.

*Feb 27* X-ray 5. Discharged.

*Mar 14* Follow-up X-ray 6.

*Comment* Three small pneumothorax treatments with partial collapse, course uninfluenced.

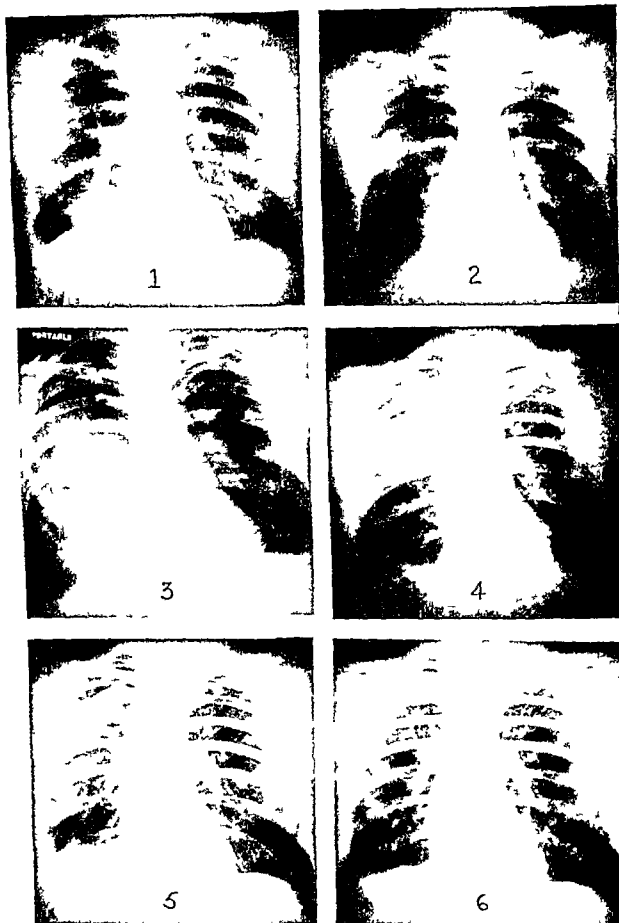


FIG 29B CASE H T SERIAL ROENTGENOGRAMS

1 pre treatment, 2 partial collapse after 750 cc of air, adhesion over upper lobe, 3 advanced consolidation 4 and 5, resolution progressing, lung expanding, 6, air completely absorbed lung re expanded

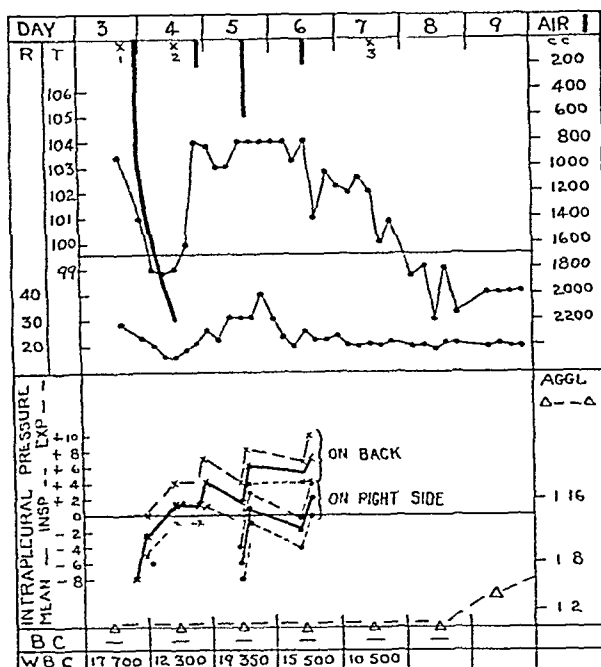


FIG 30A CASE R C

Dec 20, 1934 Onset about 6 00 p m with fever, pain in left lower chest and left shoulder, cough

Dec 21 Sputum rusty more fever

Dec 22 Temperature 103°, only moderate pleural pain, cough 5 00 p m, admitted Moderately ill, slightly cyanotic There was dullness over the left chest from the angle of the scapula to base, suppressed breath and voice sounds, fine crepitant rales 5 30 p m X-ray 1 pneumonia left lower lobe 10 00 p m, 52 hrs after onset, to 12 00 noon Dec 23, continuous injection of air with patient flat in bed and needle inserted in third left intercostal space lateral to mid-clavicular line The rate of administration with changes in pressure are as follows

10 00-11 15 p m 800 cc rate 10 7 cc per min Pressure from -8 to -4 cm

11 15-12 45 a m 625 cc rate 7 0 cc per min Pressure from -4 to -1 cm

12 45-2 50 a m Air flow stopped Position changed

2 50-8 00 a m 635 cc rate 2 05 cc per min Pressure from -6 cm on side to 0 cm on back

8 15-12 00 noon 160 cc, 0 7 cc per min Pressure from 0 to +1 5 cm

Dec 23 1 30 p m X-ray 2, incomplete collapse 8 00 p m Temperature 104° Relapse 9 40-9 50 p m, with patient on back, second air injection of 200 cc bringing mean pressure from +1 5 to +4 0 cm

Dec 24 2 30 to 2 50 p m with patient on back, mean pressure +1 5 cm, patient on right side mean pressure -6 cm, a difference of 7 5 cm of water, 600 cc of air given leaving mean pressure at +1 cm with patient on side but +6 cm when rolled over on back

Dec 25 12 20 to 12 42 p m 200 cc of air given with pressure readings in two positions

Dec 26 2 00 p m, X-ray 3 complete collapse

Dec 27 Recovery by lysis Convalescence uneventful

Dec 29 X-ray 4

Jan 8 1935 X-ray 5 Discharged

Jan 19 Follow-up X-ray 6

Comment Continuous very slow administration of first treatment, illustrates importance of relation of position to intrapleural pressure, relapse following incomplete collapse

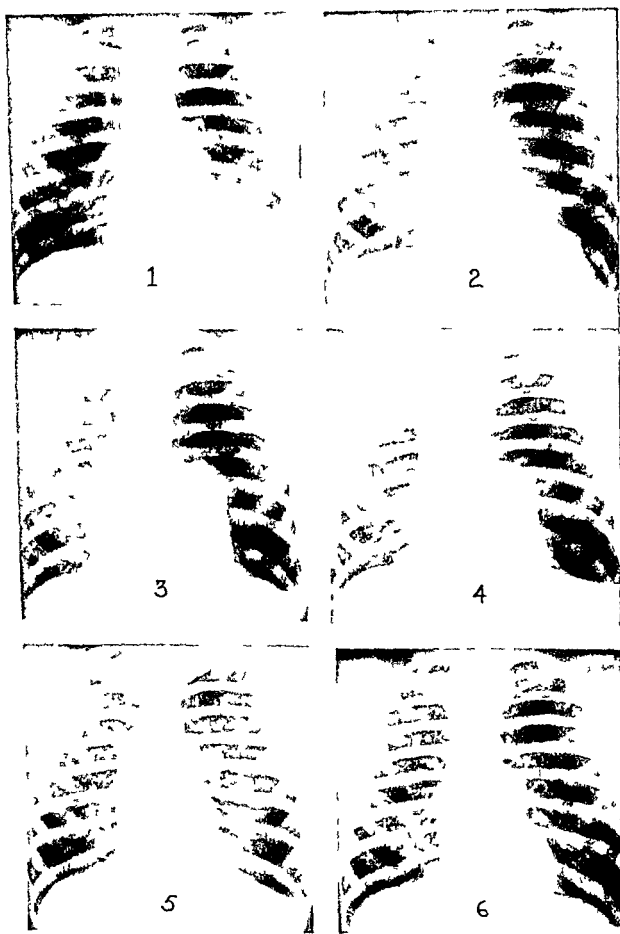


FIG 30B CASE R C SERIAL ROENTGENOGRAMS

1, pre treatment, 2, incomplete collapse after 2220 cc of air, 3, complete collapse, 4, 5, and 6, lung re expanding



NO 32532 AC ♂ 25 TYPE 1 RLL

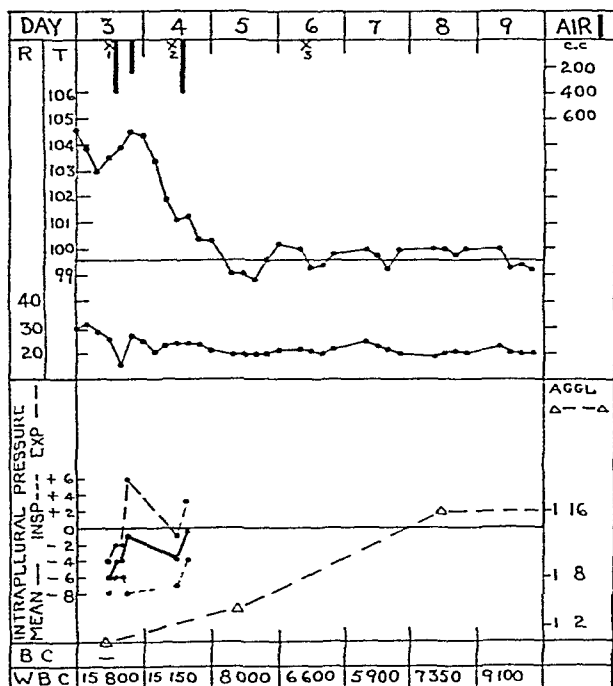


FIG 31A CASE A C

Dec 11, 1933 A m Got up but felt chilly and went back to bed P m Had a shaking chill developed pain in right chest and cough productive of rusty sputum

Dec 12 A m Worse 11 30 p m admitted Well marked cyanosis Slightly delirious Dulness over the right lower lobe, increased tactile fremitus, tubular breath sounds in the paravertebral region

Dec 13 Noon X-ray 1, pneumonic consolidation upper portion of the right lower lobe 2 40 to 3 00 p m, first pneumothorax, 54 hrs after onset, 400 cc, rate 20 cc per min mean intrapleural pressure raised from -6 to -4 cm 8 00 p m, second pneumothorax, 250 cc, mean pressure raised from -4 to -1 cm

Dec 14 11 15 a m X-ray 2, mantle pneumothorax with partial selective collapse of lower lobe 2 00 p m, third pneumothorax, 400 cc changing the mean pressure from -4 to -0.5 cm Crisis fourth day Convalescence uneventful

Dec 16 X-ray 3

Dec 20 X-ray 4

Dec 26 X-ray 5 Discharged

Jan 24, 1934 Follow-up x-ray 6

Comment First case treated, partial collapse, critical recovery but early appearance of agglutinins makes interpretation doubtful

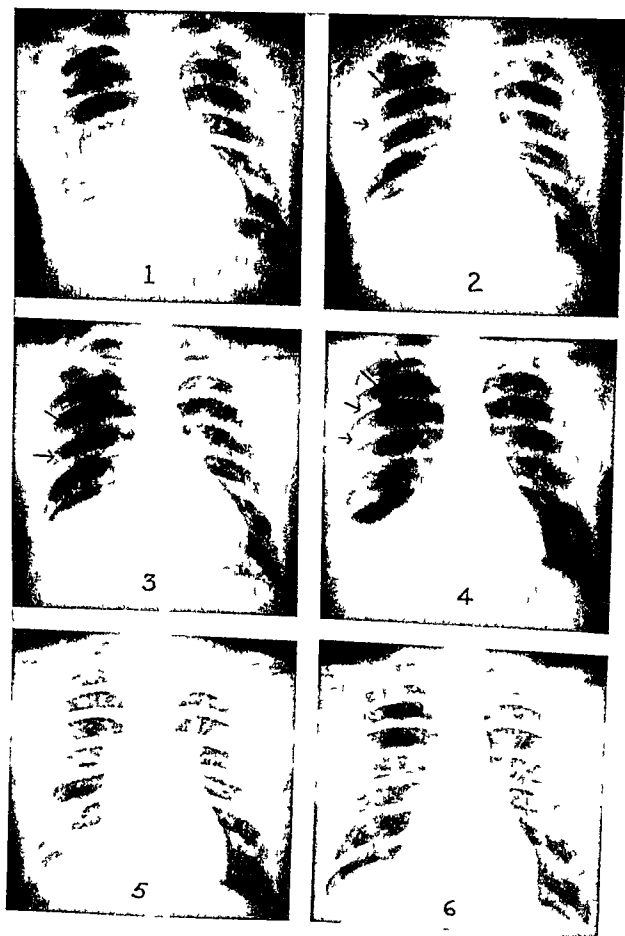


FIG 51B CASE A C SERIAL ROENTGENOGRAMS

1, pre treatment 2 and 3 mantle pneumothorax, partial selective collapse of right lower lobe, 4, beginning re expansion of right lower lobe, small pleural effusion, 5, resolution well advanced 6, air completely absorbed, lung re expanded

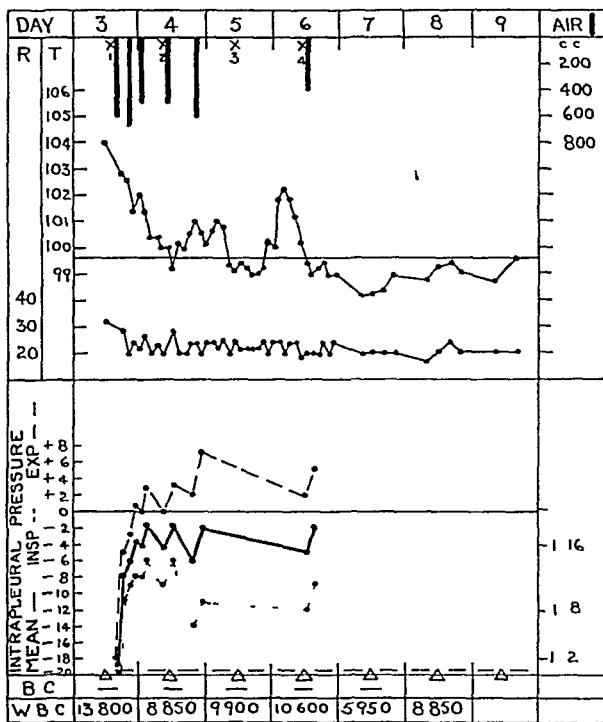


FIG 32A CASE T F

*Feb 11, 1934* Awoke in the morning with severe pain in right upper chest Denies chill, no noticeable fever

*Feb 12* Pain worse

*Feb 13* Pain worse Came to the Dispensary 1 30 p m admitted Moderately toxic Considerable cyanosis of nail beds, respirations accelerated and on inspiration there is over-expansion of the right upper chest and marked retraction of the right half of the abdomen Moderate dullness and suppression of breath sounds at the right base Few rales at right mid-axilla 3 30 p m X-ray 1, atelectasis of right lower lobe 4 14 to 4 38 p m, first pneumothorax treatment, 56 hrs after onset, patient on left side, 600 cc, rate 25 0 cc per min With the first 150 cc, the mean intrapleural pressure was built up from -19 to -5 5 cm At this point, at the end of expiration, a low crunching sound close to the needle was heard The needle was turned slowly and with the next 50 cc of air administered, the mean pressure dropped to -11 cm Final mean pressure -8 cm Marked sweating Cough troublesome 8 35 to 8 56 p m Second pneumothorax, 700 cc, rate 33 3 cc per min, bringing the mean pressure from -6 to -3 5 cm Sweating

*Feb 14* 12 55 to 1 20 a m Third pneumothorax, 500 cc, rate 20 cc per min, mean pressure brought from -4 to -1 5 cm 8 00 a m, looks well, no pain 9 00 a m X-ray 2 10 16 to 10 30 a m, fourth pneumothorax, 500 cc, rate 35 7 cc per min, with change in intrapleural pressure from -4 5 to -1 5 cm 8 40 to 8 55 p m, fifth pneumothorax, 600 cc, rate 40 cc per min increasing the intrapleural pressure from -6 to -2 cm

*Feb 15* 9 00 a m Seems well, sitting up reading 10 30 a m X-ray 3, complete collapse

*Feb 16* Transient rise in temperature 11 30 a m X-ray 4 11 55 to 12 12 p m, sixth pneumothorax 400 cc bringing the pressure from -5 to -2 cm

*Feb 17* Appears perfectly well Convalescence uneventful

*Feb 26* X-ray 5

*Feb 28* Discharged

*Mar 21* Follow-up X-ray 6

*Comment* Treated with sufficient air to cause complete collapse, prompt relief of symptoms, early recovery without development of agglutinins

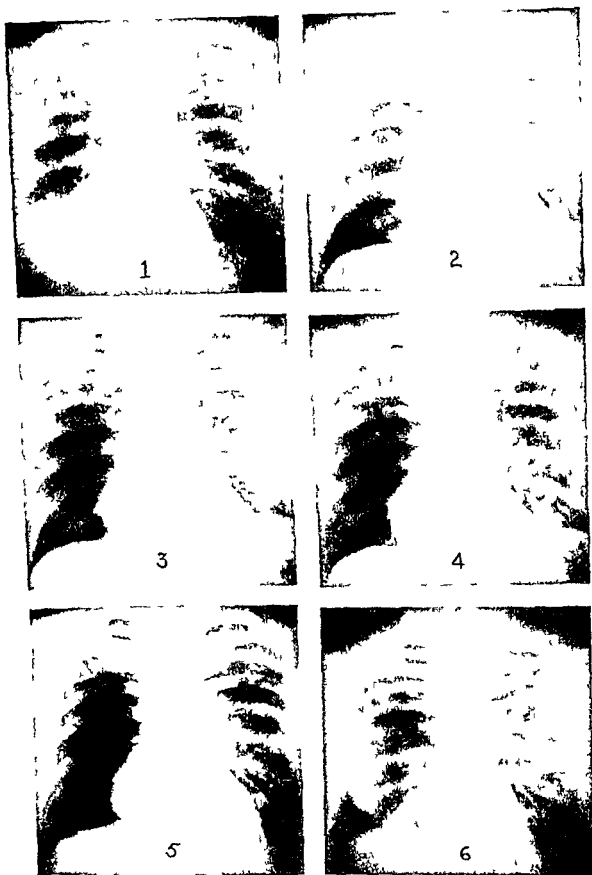


FIG 32b CASE T I SERIAL ROENTGENOGRAMS

1, atelectasis of right lower lobe presumably due to occlusion of bronchus with exudate pre treatment 2 after 3 treatments totaling 1800 cc, 3, 4, and 5, complete collapse established and maintained, 6, re expansion of upper lobe

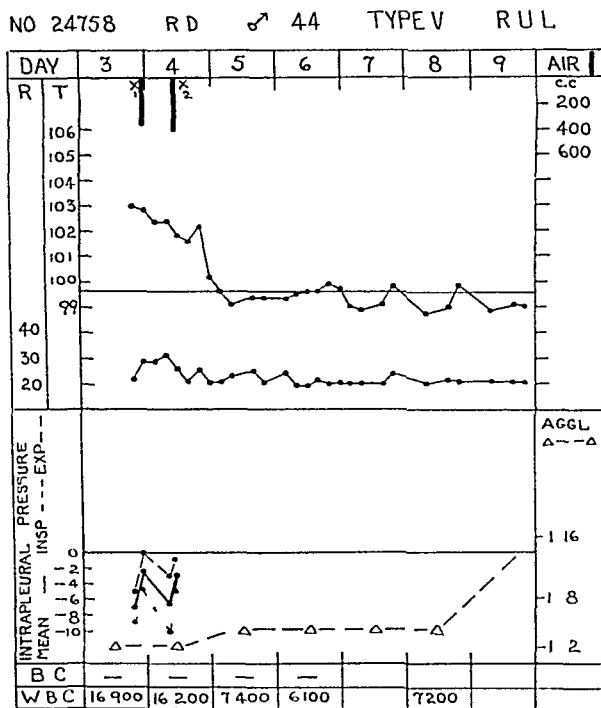


FIG 33A CASE R D

Jan 20, 1934 A m Shaking chill Pain in upper part of right chest

Jan 21 Worse Vomited in the morning Pain in lower right axilla

Jan 22 8 00 p m, admitted Acutely ill, moderate dyspnea, slight cyanosis, respirations restricted on the right Dulness over the upper lobe posteriorly and into the upper axilla where there were tubular breathing and crepitant rales Friction rub, right axilla 10 00 p m X-rays 1a and 1b 11 36 to 11 51 p m, first pneumothorax treatment, 60 hrs after onset, patient on left side, 350 cc, average rate 23.3 cc per min, with change in mean intrapleural pressure from -7 to -2.5 cm

Jan 23 10 00 a m, moderately sick, no cyanosis 10 09 to 10 26 a m, second pneumothorax, 400 cc, rate 23.5 cc per min 2 30 p m X-ray 2, mantle pneumothorax Slight cyanosis, pain in right chest

Jan 24 Crisis during night Convalescence uneventful

Feb 1 Discharged

Feb 22 Follow-up x-ray 3

Comment Critical recovery following 2 small treatments with partial collapse but early appearance of agglutinins makes interpretation doubtful

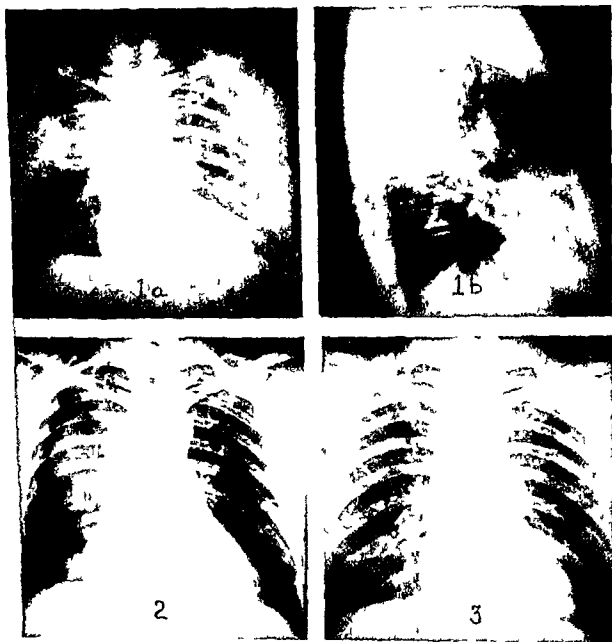


FIG 33B CASE R D SERIAL ROENTGENOGRAMS

*1a and 1b, pre treatment, 2, mantle pneumothorax after 750 cc of air, 3, air absorbed, lung re expanded*

NO 57258 JF ♂ 17 TYPE VIII LLL

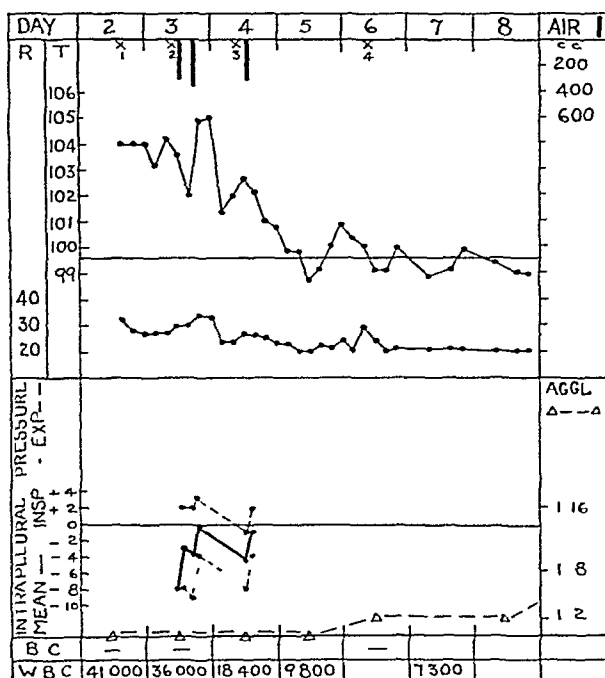


FIG 34A CASE J F

- Dec 31, 1933 2 30 p m Hot bath, then went out in cold weather to celebrate New Year's Eve 11 30 p m Shaking chill, nausea, vomiting
- Jan 1, 1934 A m Chill, pain in left chest, anorexia, cough productive of bloody sputum
- Jan 2 3 30 p m, admitted Moderately cyanotic, respirations labored Palm sized area of dullness, suppressed bronchial breathing below and medial to left scapula 4 15 p m X-ray 1, consolidation behind heart, left lower lobe
- Jan 3 A m Slight cyanosis Frank signs of pneumonia over upper half of left lower lobe behind diminished breath sounds at the base and lower axilla with numerous crepitant rales 11 30 a m X-ray 2, advancing pneumonia, left lower lobe 12 40 to 1 00 p m First pneumothorax, 61 hrs after onset, patient on right side, 300 cc, rate 15 cc per min, initial pressure -8 cm, no fluctuations, final mean pressure -4 cm 6 30 to 6 48 p m, second pneumothorax, 350 cc, rate 19 4 cc per min, changing the mean intrapleural pressure from -3 5 to -0 5 cm
- Jan 4 Much improved 9 00 a m X-rays 3a, patient erect, partial collapse, question of adhesions, 3b patient on right side, adhesions excluded 1 45 to 2 00 p m, third pneumothorax, 300 cc, rate 20 cc per min, bringing the intrapleural pressure from -4 5 to -1 cm Crisis fourth day Uneventful convalescence
- Jan 6 X-ray 4 More collapse than previously, small effusion
- Jan 9 X-ray 5, increase in effusion
- Jan 13 X-ray 6 upper lobe, re-expanding
- Jan 17 X-ray 7, further re-expansion
- Jan 19 Discharged
- Feb 19 Follow-up x-ray 8
- Comment Second case treated, prompt recovery following 3 small treatments with initial partial collapse and later complete collapse Early appearance of agglutinins leaves interpretation in doubt

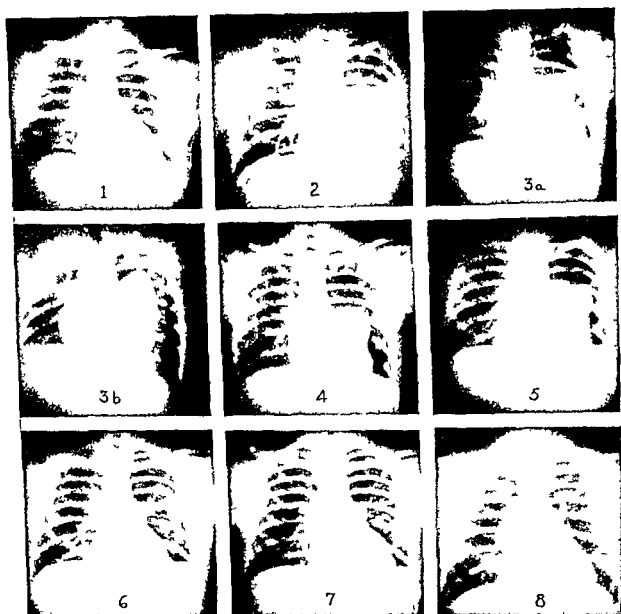


FIG 34B CASE J F SERIAL ROENTGENOGRAMS

1 and 2 pre treatment 3a partial collapse after 2 treatments totalling 650 cc of air, question of adhesions, 3b patient on right side excluding adhesions, 4 and 5, collapse maintained, small effusion developing, 6 and 7, upper lobe re expanding, 8, air completely absorbed, lung re expanded





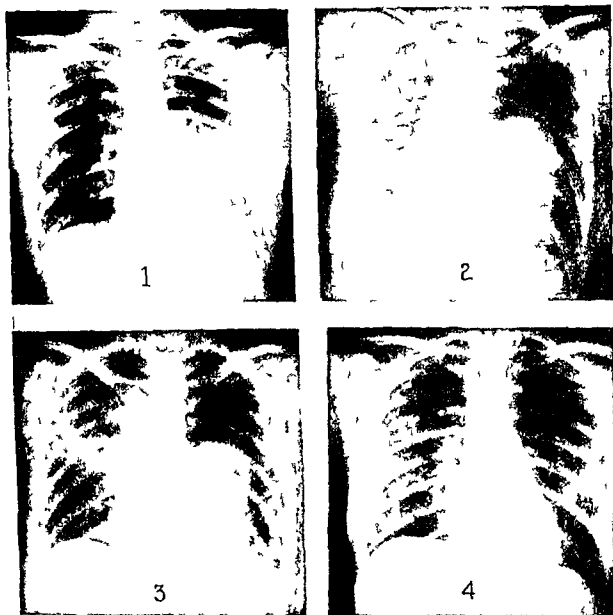


FIG 35B CASE G S SERIAL ROENTGENOGRAMS

1, pre treatment, 2, collapse following 2 treatments totalling 2100 cc of air, 3, spread to right upper lobe, 4, pneumonia resolved, lung re expanding

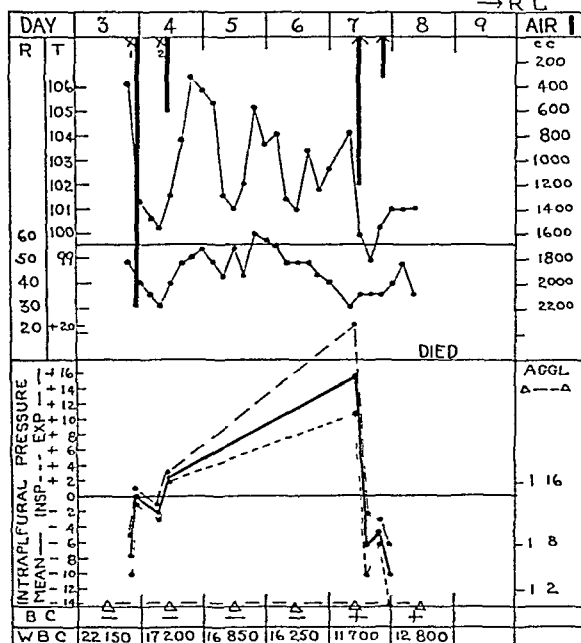
NO A53488 FM ♂ 34 TYPE 1 L L L ADH  
 → R L


FIG 36A CASE F M

- Mar 2, 1935 P m Pain in left chest, more severe on inspiration  
 Mar 3 10 00 a m Cough Nauseated and vomited P m Chills  
 Mar 4 Worse P m, fainted 7 30 p m, admitted Very toxic Splinting of left chest Signs of early consolidation over left lower lobe 8 00 p m X-ray 1 Early infiltration, upper portion, left lower lobe 11 21 p m to Mar 5, 2 50 a m, first pneumothorax, about 50 hrs after onset, patient on right side, 2200 cc, average rate 10 5 cc per min, initial mean intrapleural pressure -7 5 cm, final 0 cm  
 Mar 5 8 30 a m X-ray 2, partial collapse, adhesions 9 40 a m second pneumothorax, 600 cc, with change in mean intrapleural pressure from -2 to +2 5 cm 5 00 p m, appears worse, moderate cyanosis  
 Mar 6 Somewhat better but still sick  
 Mar 7 Quite sick, dyspneic and cyanotic  
 Mar 8 Worse Oxygen tent Spread to right lower lobe 11 39 a m Patient flat on back, mean intrapleural pressure +15 5 cm, 1200 cc of air withdrawn, reducing the mean intrapleural pressure to -6 cm Color and respirations improved Abdominal distention troublesome 9 13 p m Patient flat on back, 325 cc of air removed, lowering the mean pressure from -4 5 to -10 cm  
 Mar 9 Progressively worse 1 05 p m Died  
 Comment Severe case, partial collapse, adhesions (not well seen in X-ray picture) preventing complete collapse, subsequent spread to right lower lobe, terminal septicemia and death In retrospect this case was poorly managed With adhesions present and increasing dyspnea in evening of fourth day, an intrapleural pressure reading should have been taken at this time, air removed and Type I serum given Of 28 cases first treated earlier than 72 hrs after onset this was the only one to die

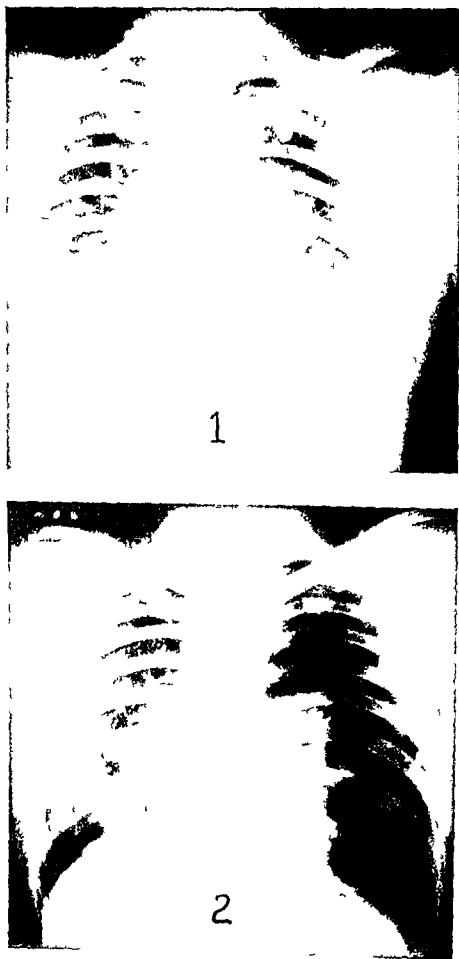


FIG 36B CASE I M ROENTGENOGRAMS  
1, pre treatment 2, partial collapse after 2200 cc of air, adhesive bands over right lower lobe not well seen in reproduction of x ray film

NO 36873 H M:V ♂ 45 TYPE VII RLL→RU

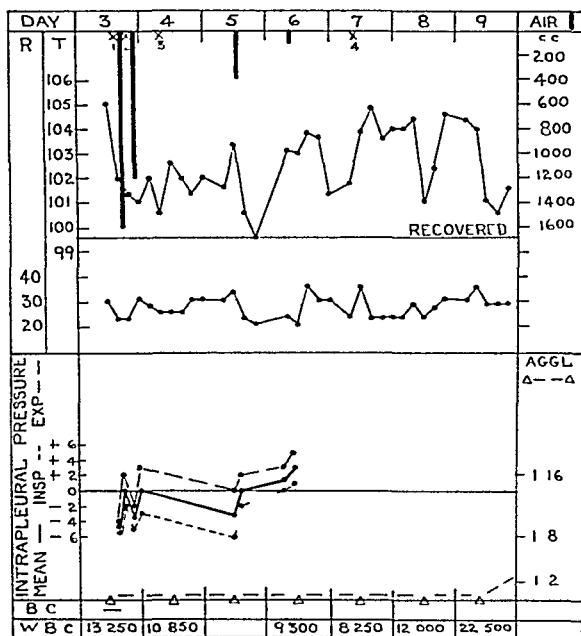


FIG 37A CASE H McV

Mar 12, 1935 Alcoholic debauch

Mar 13 Noon Awoke with pain in right lower chest P m Felt feverish

Mar 14 Chest pain worse

Mar 15 A m Sputum bloody Generalized convulsion 3 30 p m admitted  
Acutely ill Slight cyanosis Signs of consolidation at right base behind extending  
into right axilla 4 00 p m X-ray 1 5 05 to 6 13 p m, first pneumothorax treat-  
ment, about 53 hrs after onset, patient on left side, 1600 cc, average rate 23.5 cc  
per min, bringing the mean intrapleural pressure from -4.5 to 0 cm No reaction  
8 00 p m X-ray 2 Adhesions 10 37 to 11 28 p m second pneumothorax treat-  
ment, 1200 cc, rate 23.5 cc per min, with change in intrapleural pressure from -3.5  
to 0 cm

Mar 16 Delirium tremens A m X-ray 3

Mar 17 Condition unchanged 12 30 to 12 46 p m, third pneumothorax, 400 cc,  
rate 25 cc per min, bringing the mean intrapleural pressure from -3 to 0 cm

Mar 19 10 00 a m X-ray 4, spread to right upper lobe

Mar 21-23 Recovery by lysis

Mar 24 Improvement in mental symptoms with fall in temperature

April 4 Discharged

Comment Failure of artificial pneumothorax to influence course of disease in case with  
adhesions preventing adequate collapse of right lung

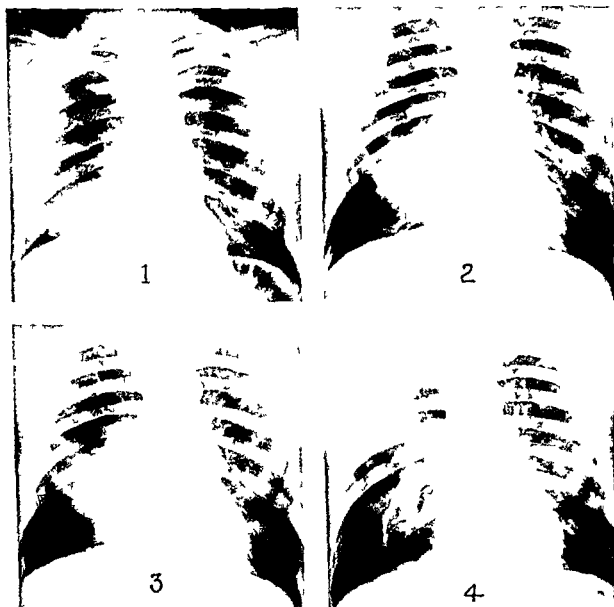


FIG 37B CASE H McV SERIAL ROENTGENOGRAMS

1, pre treatment, 2 and 3, local pneumothorax, extensive adhesions, 4, spread to right upper lobe

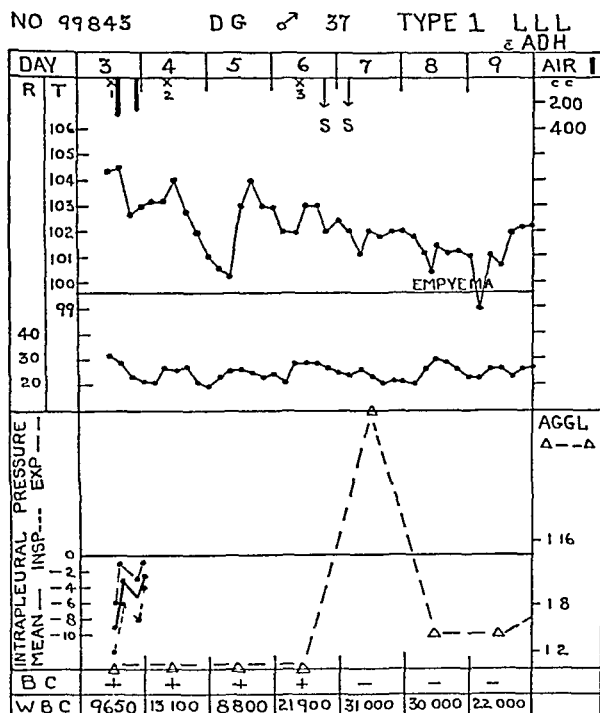


FIG 38A CASE D G ALCOHOLIC LEFT-SIDED PLEURISY IN 1931

- Jan 17, 1934 A m Shaking chill with persistent chilliness throughout the day  
 Jan 18 A m Pain in left lower chest anteriorly and in left shoulder P m, nausea and vomiting Cough productive of green sputum  
 Jan 19 12 15 p m, admitted Face flushed Signs of consolidation at left base behind, extending into lower left axilla 1 30 p m X-ray 1 3 20 to 3 33 p m First pneumothorax treatment, about 56 hrs after onset, patient on right side, 300 cc, average rate 23.1 cc per min, initial mean pressure -9 cm, final mean pressure -3.5 cm Vomited twice 9 43 to 9 55 p m, second pneumothorax, 250 cc, average rate 20.8 cc per min, changing the mean intrapleural pressure from -5.5 to -2.5 cm No reaction  
 Jan 20 9 30 a m X-ray 2, adhesions General condition fairly good  
 Jan 22 Worse Signs of fluid at left base, question of spread to right 11 00 a m X-ray 3, fluid at left base 6 30 p m Type I serum 60,000 units Thoracentesis, 10 cc moderately cloudy, amber fluid Culture, pneumococcus Type I  
 Jan 28 Thoracotomy Stormy post-operative course with delirium tremens  
 Feb 3 X-ray 4  
 Apr 16 X-ray 5  
 May 5 Discharged Draining fistula  
 Oct 1 Entirely recovered X-ray 6  
 Comment Severe alcoholic with heavy bacteremia Sixth case in the series, two small pneumothorax treatments, numerous adhesions, bacteremia checked by Type I serum, empyema, eventual recovery

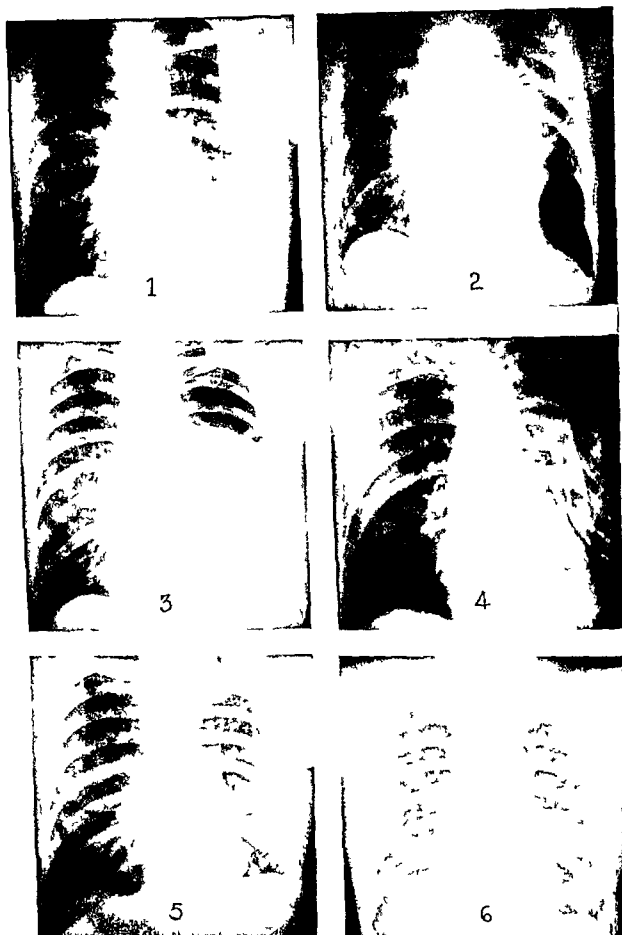


FIG 38B CASE D G SERIAL ROENTGENOGRAMS

1, pre treatment, 2, adhesions, local pneumothorax, 3, empyema, 4 and 5, drainage of empyema, 6, lung re-expanded





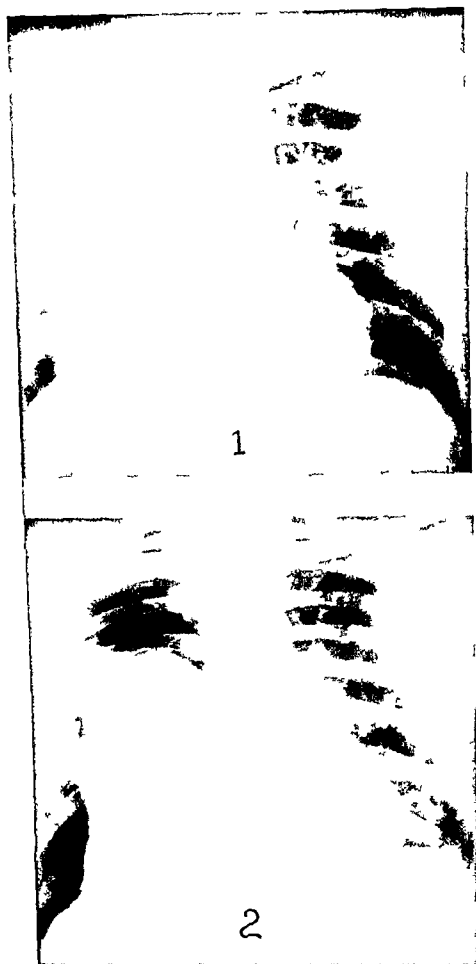


FIG 39B CASE R P ROENTGENOGRAMS  
1 pre treatment, 2, adhesions, further treatments contraindicated

NO 96587 SC ♀ 36 TYPE V RLL &amp; ADH

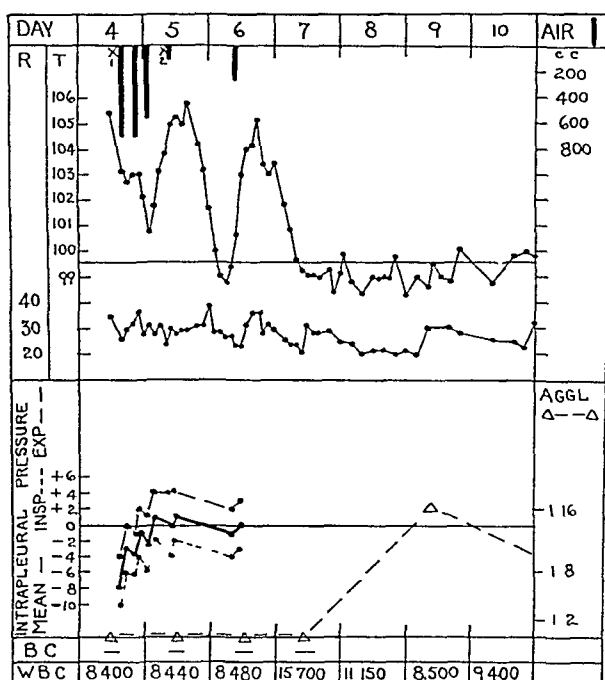


FIG 40. CASE S C

April 2, 1934 6 00 a m Awoke with shaking chill, chilly all morning Fever to 105°  
Vomited

April 3 Fever 105° Dyspneic Pain in right chest on breathing

April 4 Condition the same

April 5 Cough 12 00 noon, admitted Acutely ill Moderately dyspneic, prostrate  
Moderately cyanotic Chest expansion limited on right, dullness over RLL with  
bronchovesicular breathing behind, increased fremitus and fine rales Breath sounds  
suppressed in axilla 1 00 p m X-ray 1, advanced consolidation of RLL 4 14  
to 4 29 p m, first pneumothorax, about 82 hrs after onset, patient on left side, 700 cc  
of air given at rate of 46.6 cc per min, raising the mean intrapleural pressure from  
-7 to -3 cm 9 04 to 9 20 p m, second pneumothorax, 700 cc, rate 43.8 cc per  
min, changing the pressure from -3.5 to -2 cm

April 6 1 15 to 1 33 a m, third air injection, 550 cc, rate 30.6 cc per min, bringing  
the mean pressure from -2.5 to +1 cm 9 00 a m X-ray 2, extensive adhesions  
9 30 to 9 35 a m Pressure readings before and after the administration of 100 cc of  
air 0 to +1 cm No change in general condition

April 8 10 00 a m Seemed improved 10 30 to 10 38 a m, fifth pneumothorax,  
250 cc, which raised the pressure from -1 to 0 cm Crisis during night Convalescence uneventful

April 14 X-ray 3, beginning re-expansion

April 21 X-ray 4 Discharged

May 30 Follow-up x-ray 5

Comment Advanced case with adhesions Artificial pneumothorax failed to influence  
the course of the disease

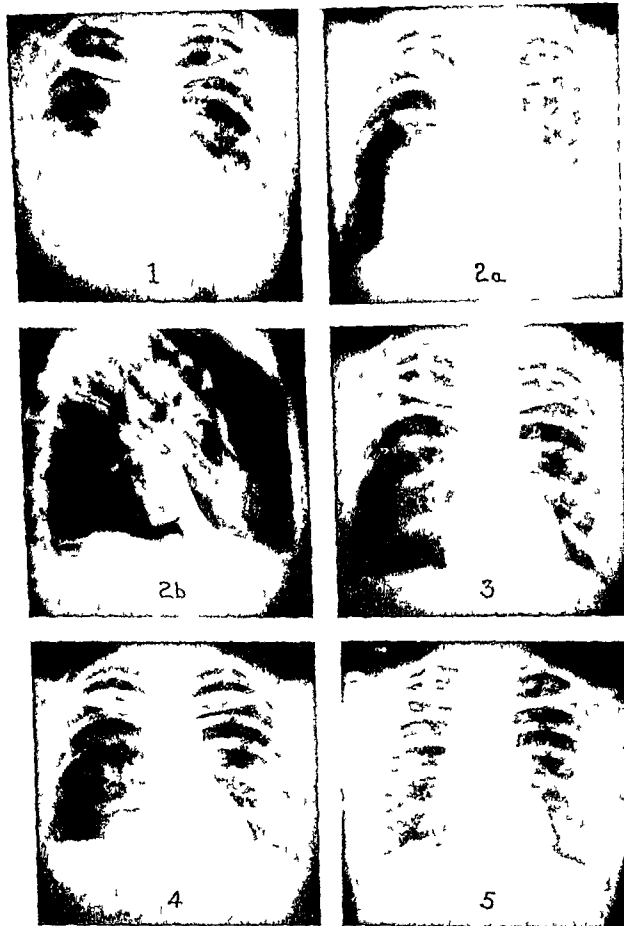


FIG 40B CASE S C SERIAL ROENTGENOGRAMS

1 pre treatment, 2a and b, localized pneumothorax extensive adhesions 3 and 4, resolution small pleural effusion, 5 air completely absorbed, lung re-expanded

NO 96587 5

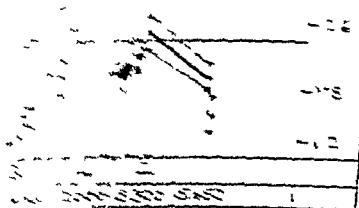
DAY		4
R	T	
	106	
	105	
	104	
	103	
	102	
	101	
	100	
	99	
40		
30		

$\Delta p_{ri}$   
 $V_0$

$\Delta p$

$\Delta p$

$\Delta p$



rusty sputum, headache, dyspnea

moderate dyspnea slight cyanosis  
 lower lobe with loud pleural  
 friction rub first pneumothorax trace  
 5 to 10 cc per min (includes

average rate 12.5 cc  
 cm. 6:35 to 7:08

heart mean pressure 1.0  
 1.0 between right  
 and left

Frank signs

chest x-ray  
 6:35 to 7:08

chest x-ray  
 6:35 to 7:08

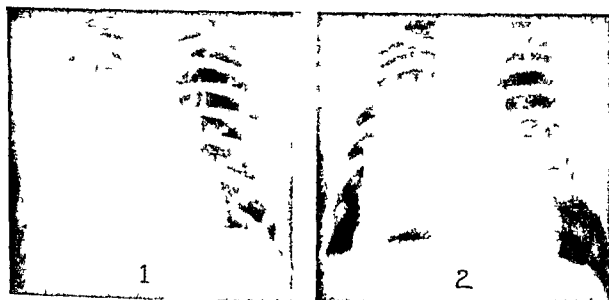


FIG 41B CASE R CO ROENTGENOGRAMS

1 pre treatment advanced consolidation of right lower lobe, 2 mantle pneumothorax, adhesion between lower lobe and diaphragm, spread to left lower lobe

NO A33345 J L ♂ 77

TYPE VIII LUL

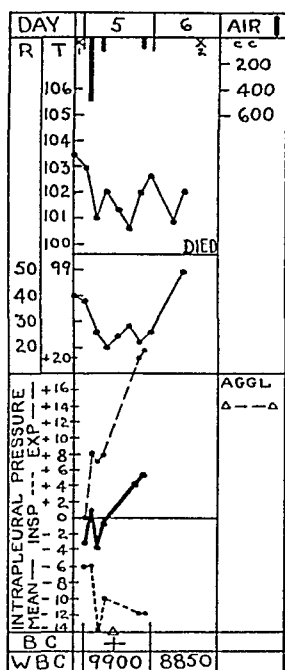


FIG 42A CASE J L COLD AND COUGH OF 2 WEEKS' DURATION

*Mar 6, 1934* Worse Dyspneic Sputum bloody

*Mar 8* P m, sharp pain left lower axilla, relieved by plaster

*Mar 9* Increase in weakness, cough, dyspnea 9 20 p m, admitted Respirations noisy and shallow Slight cyanosis Generalized arteriosclerosis Arteriosclerotic heart disease, auricular fibrillation Emphysematous chest Dulness over left mid-front extending high into left axilla Breath sounds tubular in front, suppressed in axilla

*Mar 10* 12 00 m X-ray 1, pneumonic consolidation lower portion of left upper lobe 1 26 to 2 15 a m First pneumothorax treatment, about 90 hrs after onset, patient on right side, raising the mean intrapleural pressure from -3 to +1 cm, rate 10 2 cc per min 5 58 a m, second pneumothorax, 100 cc, increasing mean pressure from -3 5 to -1 cm 7 00 a m Patient quite cyanotic, radial pulses almost imperceptible Oxygen tent 8 34 to 8 41 p m Pressure readings show mean pressure to be +4 to +5 cm

*Mar 11* Grew progressively worse all day Died at 3 40 p m X-ray 2, post-mortem Post-mortem examination Diffuse pneumonia, LUL Focal pneumonia, RML Serofibrinous pleurisy, left, fibrinous pericarditis Generalized arteriosclerosis, myocardial fibrosis, fibrous pleural adhesions, right

*Comment* Advanced septicemic case, artificial pneumothorax of no value

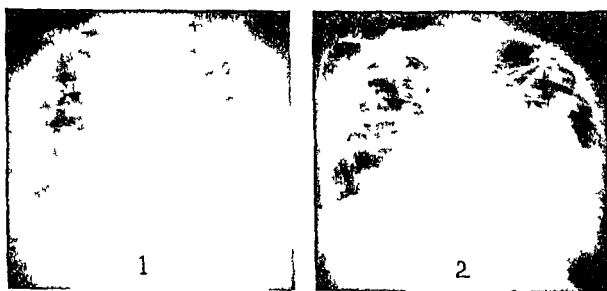


FIG 42B CASE J L ROENTGNOGRAMS  
1, pre treatment, 2, postmortem





# THE TREATMENT OF HUMAN BRUCELLOSIS

## A REVIEW OF CURRENT THERAPEUTIC METHODS

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An attempt to evaluate the effectiveness of therapeutic agents for the treatment of human brucellosis encounters to an unusual degree the difficulties inherent in the analysis of clinical data. This is true for several reasons, of which the frequent occurrence of either remissions or spontaneous recovery is the most important. Another difficulty is the validity of a diagnosis which rests only on the presence of a febrile syndrome and brucella agglutinins. Such evidence does not constitute a reliable diagnosis, because the agglutinins may have been the result of a previous subclinical infection. In fact, this is not uncommon, especially in rural districts. Furthermore, brucella agglutinins may have been produced by an anamnestic reaction initiated by a febrile response to some other infectious agent. In some reported instances, a positive skin test was the only specific evidence on which the diagnosis was based. From our present knowledge of antigens available for intradermal tests, such evidence alone is insufficient, especially when 20 per cent of the residents in certain communities show a positive reaction to the test (1). In addition to fever and a positive agglutination test, the presence of certain other findings, such as, for example, a possible source of infection, general malaise, night sweats, weakness, depression, secondary anemia with a low normal white blood cell count or a leukopenia with a relative lymphocytosis, positive intradermal test, and exclusion of other diseases, makes the diagnosis unquestionable. A history of undulant fever, also, might be considered to be an aid in classifying the disease, since recurrences are not infrequent. The isolation of the organism establishes the diagnosis of brucellosis beyond doubt, but the frequency of failure

to recover it makes the recognition of the disease depend upon other findings in most instances

This report includes a survey of the literature on the treatment of human brucellosis, and the results of our own experiences with therapeutic agents employed for the relief of this disease. No attempt has been made to differentiate between infections caused by bovine, by porcine, or by caprine strains, since all members of the genus *Brucella* bring about the same tissue response. The entire literature on therapy has been reviewed, but most of the facts recorded in this report have been selected from 67 original contributions. No consideration has been given to the medicinal agents used for the relief of such symptoms as pain, sweating, or constipation, drugs designed for the immediate comfort of the patient. This discussion is concerned with only vaccines, serums, toxic filtrates, and chemicals, that is, agents which are employed for their specific immunological and bactericidal activities. An endeavor was made to evaluate each agent on the basis of the average duration of illness, and especially on the time required for the relief of symptoms after treatment was instituted. A study of the literature has revealed, however, the shortcomings of such an appraisal, because of the meager information submitted by most authors. Summaries and general statements as to the efficacy of this or that treatment abound, and comprise all the information available in most cases.

A wide variation in the duration of illness is characteristic of undulant fever. Deaths from this disease are infrequent, but its morbidity may be severe. It is difficult for the patient or the physician to state the exact length of illness in any chronic infectious disease, and especially so in undulant fever, because of the gradual onset and the slow convalescence. A study of the cases reported in the literature, and those observed personally, however, shows the average duration of the disease to be about 3 months. The extremes range from 10 days to 6 months, and occasionally recurrences of symptoms may continue for 6 or more years. Hughes (2), in 1897, stated, "It may be safely said that the average pyrexial duration exceeds 60 or 70 days, while cases have been known to exceed 300 days." Bassett-Smith (3) stated that in 1904 there occurred in the British Navy, 430 cases of undoubted *Brucella melitensis* infection, totalling 28,458 days of

illness, which is an average of 66 days of sick leave for each patient. He observed the average duration of melitensis infection to be 4 months. Hardy (4) reported that the average period of incapacitation for 212 patients with *Br abortus* infection was about 3 months. He states, "The percentage by periods are as follows. One month or less, 19 per cent, 1 month to 10 weeks, 27 per cent, 3 to 4 months, 34 per cent, 5 to 6 months, 11 per cent, more than 6 months, 9 per cent."

Since few clinical cases of undulant fever are untreated, the therapeutic value of specific treatment, *ie*, by serums, vaccines, toxic filtrates, and chemicals, can best be obtained by comparing a group of patients subjected to such therapy with a group treated symptomatically. Although symptomatic treatment may shorten the course of a disease, a group of cases so treated may serve as a control, because such treatment has little influence on the natural antigen-antibody relationships.

A summary of 26 cases of brucellosis treated symptomatically, of which 18 were observed at the Strong Memorial Hospital, Rochester, New York, and 8 treated elsewhere, is presented in table I. Only uncomplicated cases of undulant fever are included. *Br abortus* was isolated from the blood of about 30 per cent of the group. With the exception of 2 cases, recently observed, all have been followed for from 1 to 10 years. The duration of illness varied from 2 to 72 weeks, with an average of 12.5 weeks. Three deaths have occurred in this group, of which only 1 was due to undulant fever. Seven patients have had recurrences of symptoms which, with one exception, have been mild, and in some instances, questionable. None has required hospitalization or the care of a physician during these recurrences. The following report illustrates a typical case and the type of symptomatic medication received by patients in this group.

M. A., a 40-year-old moderately obese Jewish man, was admitted to the hospital, March 2, 1931, complaining of fever. His present illness, which began 6 weeks before admission, was first diagnosed as "la grippe." Weakness and fever had been present until the time of admission. His past history was unimportant. Physical examination showed the temperature to be 37.8°C, pulse, 90, respiration, 24, blood pressure, 110 systolic, 60 diastolic. Except for general weakness, mental depression, and general apathy, the physical examination was negative. The laboratory findings

were as follows Hemoglobin, 75 per cent, red blood cells, 3,750,000, white blood cells, 5,300, urine, negative, x-ray of sinuses, negative, x-ray of chest,

TABLE I

*Duration of illness and period of observation in 26 cases of undulant fever treated symptomatically*

PATIENT	LENGTH OF ILLNESS	PERIOD OF OBSERVATION	REMARKS CONCERNING PRESENT STATUS
	<i>weeks</i>	<i>years</i>	
R B	6	10	Occasional cervical lymphadenitis and synovitis of right knee during first 5 years
C T	2	9	No recurrence of symptoms
R G	7	9	No recurrence of symptoms Died from intestinal obstruction
R F	7	8	Several mild recurrences of fever during first year
H G	11	8	No recurrence of symptoms
R W	6	8	No recurrence of symptoms
L M	7	7	No recurrence of symptoms
E F	8	6	No recurrence of symptoms
P G	7	6	Tired easily for 2 years
P R	3	6	No recurrence of symptoms
F Lu	20	5	No recurrence of symptoms
M Ab	28	5	No recurrence of symptoms
M Ph	8	5	No recurrence of symptoms
M Ar	8	4	No recurrence of symptoms
W Hv	20	4	No recurrence of symptoms
G An	8	3	Tonsillectomy <i>Br abortus</i> isolated from tonsils No recurrence of symptoms
L C	7	3	Annual recurrence of fever in spring for 3 years
A B	26	2	Recurrence of mild symptoms 18 months later
H H	22	2	Recurrence of mild fever during first year
J N	2	2	No recurrence of symptoms
W <sub>1</sub>	3	2	No recurrence of symptoms Died—accidental drowning
E H <sub>1</sub>	11	1	Slight fever and backache three months later
L McE	72	1	Several recurrences of fever during first year Died from endocarditis
J P	3	1	No recurrence of symptoms
E Ha	14	4 months	Afebrile, but still weak
D H	10	3 months	Afebrile, at present, but recovering from secondary anemia, psychosis, and weakness

definite clouding at the apices, Wassermann, negative, serum titer, 1 to 360 with *Br abortus* antigen, blood culture, negative The course in the

hospital was uneventful The patient was febrile until 7 days before discharge on March 17, 1931 He received the following treatment

- 3/ 2/31 Ephedrine inhalant, 2 drops, every 3 hours  
Acetanahd, 0 20 gram, every 3 hours, when necessary
- 3/ 3/31 Pyramidon, 0 650 gram
- 3/ 4/31 Acetanahd, 0 20 gram
- 3/ 5/31 Fluid extract, cascara segrada, 4 cc , 3 times a day, after meals,  
and at night  
Barbital, 0 325 gram
- 3/ 6/31 Tomato juice, daily  
1 Harris yeast tablet, 3 times a day  
Pyramidon, 0 325 gram
- 3/ 7/31 Blands pills, 0 325 gram, 3 times a day  
Liver once a day
- 3/ 8/31 Sulfonal, 0 65 gram, in 15 cc hot whiskey  
Codeine, 0 030 gram  
Pyramidon, 0 650 gram
- 3/10/31 Luminal, 0 097 gram in hot milk at bed time
- 3/11/31 Quinine, 0 2 gram, every 3 hours  
Barbital, 0 325 gram, at bed time
- 3/12/31 Luminal, 0 097 gram, at bed time
- 3/13/31 Trional, 0 325 gram, at bed time
- 3/15/31 Barbital, 0 650 gram, at bed time

The therapeutic methods employed for the treatment of undulant fever are considered under the following headings (1) vaccine therapy, (2) serum therapy, (3) therapy with toxic filtrates, (4) chemical therapy, (5) foreign protein therapy, (6) therapy with artificially induced fever, (7) mixed therapy

#### VACCINE THERAPY

Since vaccine therapy has been most extensively employed for treating human brucellosis, we shall consider it first Twenty-seven of the 67 original reports, which we have reviewed, were concerned with the use of a vaccine which was prepared from stock or autogenous strains of either or both *Br abortus* and *Br melitensis* The various reports included data on from 1 to 95 cases, with a total of 350 patients

Wright (5) first prepared and used a heat killed vaccine, made from a culture of *Br melitensis*, for the treatment of undulant fever It is

often referred to as "Wright's vaccine" Other early work on vaccination was undertaken by Bassett-Smith, who made 3 reports The first (6), which appeared in 1912, described the treatment of a patient who, after an illness of 4 months, was given 7 injections of from 100 to 500 million organisms at 5- and 7-day intervals His temperature became normal after the second injection, and remained so for the 5 weeks during which he was observed In 1921 (7), he treated 2 cases of "paramelitensis" infection with a heat killed-vaccine, prepared from a culture evidently identified at that time as *B paramelitensis* The injections were given after illness had existed for many months One recovered, while the other died, after receiving 5 increasing doses of the vaccine, beginning with 250 million organisms Marked local and general reactions, including generalized purpura, occurred in the fatal case Later (3), in the same year, he reported on the treatment of 61 cases with a stock melitensis vaccine, made from recently isolated strains His summary states,

. in acute cases with much autoinfection little or no good was derived from vaccine therapy, but in more chronic forms with irregular or slight temperature there was a distinct benefit In some, when vaccines were given on a rising wave, this fever was cut short and permanently kept down Since these investigations were made I have generally used vaccine and often with good effect, substituting a sensitized for the ordinary vaccine, but I still think that with very high temperature the vaccine should not be given.

This advice was given 15 years ago, but it is still sound

Owen and Newham (8), in 1915, treated 1 case of undulant fever with 4 injections of an autogenous vaccine, given 2 months after the onset The patient improved, but during convalescence developed pneumonia, from which he recovered He was discharged from the hospital 4 months later Caronia (9), in 1917, treated successfully 8 cases of undulant fever with a lysed vaccine, a type which he believed he had previously proved to be valuable in the treatment of enteric fevers Each patient was given from 2 to 5 intramuscular injections of 1 cc each of the vaccine from 2 to 12 weeks after onset of the disease Within a week, defervescence had occurred in all the patients, while other symptoms as well had subsided in 2 others, 1 of whom had received the vaccine intravenously, the other, 1 intravenous

and 1 intramuscular injection Caronia prepared his vaccine by incubating a saline suspension of the organisms with human antimeli-tensis serum for 36 hours at 37°C After the addition of more anti-serum, reincubation was repeated as above After adding 0.5 per cent of phenol, the suspension was slowly centrifuged Subsequently, the supernatant fluid, which constituted the vaccine, was heated for 1 hour at 55°C on each of 3 consecutive days

Caronia's vaccine was employed in 1918 by Chiriaco (10) on 3 cases with satisfactory results DeFinis (11), in 1923, reported the cure of 55 cases of undulant fever, probably of caprine origin, with a vaccine prepared from stock strains of *Br melitensis*, according to Caronia's method He summarized his results by stating that the majority of his patients improved immediately after use of the vaccine, and that in some cases defervescence occurred by crisis The fever of those who failed to respond immediately soon returned to normal by lysis Furthermore, the enlarged livers and spleens rapidly resumed their normal sizes Usually, a slight febrile reaction occurred after injection of the vaccine

We have had no experience with this type of vaccine but the brilliant results reported by 3 investigators from its use on 66 cases, without a single failure, should prompt others to employ it

An unfavorable experience with the use of a vaccine was noted by Alfred-Coury (12) in 1922 One of 2 cases treated with "Wright's vaccine" died in 24 hours from a hyperpyrexia (42.5°C), while the other refused to continue its use because of a severe systemic reaction following the first injection

Courcoux, Lelong and Cordey (13), in 1922, unsuccessfully treated 1 patient, 3 months after onset, with a heat killed autogenous vaccine Dargein and Plazy (14) reported unfavorably on the vaccine treatment of 9 cases Seven officers, whose infection originated from an aborting bitch, derived no benefit from injections of from 50 to 200 million heated organisms obtained from autogenous cultures Each of 2 infected laboratory workers was subjected to large doses of a vaccine sensitized with autogenous serum Each received doses of from 500 million to 6 billion bacteria In one, the duration of the disease may have been shortened

In studying the value of the oral administration of vaccines, Nicolle



and Conseil (15), in 1922, treated one patient experimentally injected subcutaneously with 450 millions of living *Br melitensis* organisms. Symptoms developed in 17 days, but agglutinins could not be demonstrated in the blood serum for a month. They state that daily vaccine treatments of this patient by mouth resulted in a cure. This statement seems unwarranted because of such meager evidence.

Khaled (16), in 1923, used a heat killed *Br abortus* vaccine for the treatment of 3 cases of *Br melitensis* infection, believing that it would be less toxic than one of caprine origin. Six subcutaneous injections, containing 300, 600, 800, 1,000, 1,500, and 2,000 million organisms per cubic centimeter, were administered at 5-day intervals. In only 2 instances was the length of illness previous to treatment given,—2 5 and 29 weeks, respectively. The former patient became afebrile in 26 days, the latter was reported to have improved. The temperature of the third case returned to normal 37 days after treatment was discontinued.

Sergeant, Mignot and Kourilsky (17), in 1926, described the recovery of 1 case of undulant fever after the administration of an antimelitensis vaccine, prepared by Ranque and Senez and called "vaccin iode." Keefer (18), in 1924, reported the first case of undulant fever due to *Br abortus* in the United States. Vaccine therapy was employed without benefit. Arloing and Langeron (19), in the same year, observed an "Arthus phenomenon" after injecting, subcutaneously, 250 million heat killed organisms into a patient ill 2 5 months with the disease. His temperature became normal in 24 hours, and after 4 weeks' convalescence, he recovered completely.

Kristensen (20), in 1928, commented favorably upon the use of abortus vaccines, but gave no data. He recommended the method of vaccination used by Parisot and Simonin (21). It was Kristensen's impression that vaccines have no specific effect, and are of no more value than foreign proteins.

In 1929, Angle (22) reported on the treatment of 10 cases of undulant fever with a heat killed vaccine. This was prepared from bovine and porcine strains of *Br abortus* and contained 6 billion organisms per cubic centimeter. Subcutaneous and intramuscular injections of from 0 25 to 1 cc were given at intervals of from 2 to 3 days. The treatments were administered from the second to the

twenty-sixth week after onset of symptoms. As a rule, a systemic reaction occurred, followed by complete defervescence in from 1 to 3 weeks. Recently the same worker (23) gave a similar vaccine to 95 cases. Of these, 84 were hospitalized for an average period of but 22 days. Eleven per cent had a recurrence. One patient with cholecystitis failed to improve, while 2 died from subacute bacterial endocarditis. Simpson (24), in 1930, reported favorable results in 46 cases injected with a suspension containing 2 billion heat-killed organisms per cubic centimeter. Hansmann and Schenken (25), in 1932, described a fatal case of meningoencephalitis, due to a porcine strain, that had been treated with autogenous and stock vaccines early in the course of the disease.

Poppe (26), in 1933, had excellent results in 16 of 20 cases treated with from 8 to 10 intramuscular injections of a heat killed vaccine containing 10 million bacilli per cubic centimeter. One-half cubic centimeter of the suspension constituted the first injection, which was gradually increased to 2 cc. He observed that the best results were obtained when a systemic reaction followed the injections. O'Neil (27) prepared a detoxified vaccine by treating cultures of *Br abortus* with nitrous acid. Five patients, injected subcutaneously with doses graduated from 0.05 to 0.5 cc. of a suspension containing 200 million organisms per cubic centimeter, made satisfactory recoveries without experiencing severe reactions. Beattie and Rice (1), in 1934, reported the successful vaccine treatment of 3 cases.

During the last year, several investigators have observed better results from injecting vaccines intravenously than by other routes. Guigni (28) noted marked systemic reactions after intravenous administration, followed by rapid defervescence and disappearance of splenomegaly. Initial injections of from 5 to 10 million bacteria were given, followed after from 2 to 5 days by doses which increased from 50 to 300 million organisms. Eight to 10 injections resulted in complete cures. The doses employed did not cause too severe reactions, even when used on very ill patients. Bianchi (29) recommended the intravenous use of vaccines, and stated that 20 cases had been completely cured.

The results described by Caronia (9) and by DeFinis (11), from the use of lysed vaccines for *Br melitensis* infection, were the most

spectacular Although the periods of convalescence and observation after treatment were not stated, these patients became afebrile in from 1 to 7 days after treatment Only mild reactions occurred after the injections, and no failures or deaths were reported

It is evident from this review that attributing favorable results in the treatment of undulant fever to a specific effect of vaccines is not justifiable It seems to us to be more probable that their value is dependent upon the intensity of the generalized systemic reaction evoked by their injection The type of vaccine used, apparently, has little to do with the outcome The toxic effect of vaccines may be dangerous, which demands conservatism in their use

#### SERUM THERAPY

Of a total of 67 reports, only 13 discuss the use of serum therapy, which, of course, has been employed more extensively than the published accounts indicate Human convalescent serum, and various animal antisera, prepared against strains of *Br abortus* and *Br melitensis*, have been used Wright (5) pioneered also in the serotherapy of brucellosis He prepared an antimelitensis horse serum which Aldridge (30) used for the treatment of 5 cases, the results of which were reported in 1898 Aldridge refers to the serum as an "antitoxic plasma" Two cases did not improve when treated in the sixth and ninth weeks, respectively, of their illness A third, given the serum in the seventh week of the disease, improved temporarily, but relapses occurred The remaining 2 cases received several injections of the antiserum early, and appeared to derive benefit from the treatment Eyre (31), in 1908, made the following statements on the use of antiserum

In 1895 Wright infected goats and in 1896 a horse was inoculated with *Micrococcus melitensis* in the attempt to produce an antiserum, and about 50 cases seem to have been treated with the serum from the horse (Aldridge, Fitzgerald, and Ewart), but the published cases do not offer any very convincing evidence of the value of such serum

Trambusti and Donzello (32), in 1909, reported favorable results from the use of an antimelitensis goat serum Kristensen (20), in 1928 treated 10 cases of undulant fever, probably due to *Br abortus*,

with an antimelitensis horse serum, 8 of which improved, while 2 failed to respond. A bovine antiabortus serum was administered to 7 other patients, which cured 4, but failed to modify the course of the disease in 3. Baker (33), in the same year, reported on the use of human convalescent serum on 1 case, which improved temporarily, but later had recurrences. Modinos (34), in 1929, treated a boy with 2 subcutaneous injections of a blister fluid obtained with a cantharides ointment, and states that he recovered rapidly.

Recently, the development of a more potent antiserum has engaged the attention of several investigators. O'Neil (27), in 1933, reported excellent results in treating 3 cases of undulant fever with a goat antiserum produced by cultures treated with nitrous acid. In the following year, Beattie and Rice (1) reported the treatment of 3 cases with the serum prepared by O'Neil which became afebrile in 2 days, 1 week, and 2 weeks, respectively, making the average duration of illness 4.5 weeks. Wherry, O'Neil and Foshay (35) later described the results of treating 26 cases with a serum developed by injecting goats with formalin killed cultures subsequently detoxified with nascent nitrous acid. Three daily injections of 20 cc each of the serum were given by vein, intramuscularly, or subcutaneously. Twenty selected cases, sick on the average for about 8 weeks prior to serum therapy, responded well. The average duration of disability was about 11 weeks. The inclusion of 4 cases which failed to improve, and of 2 in which the results were doubtful, would markedly increase the average duration of the disease from such therapy. Mitchell, Humphreys and Walker (36) developed an equine antiserum with a titer of 1 to 320,000, which was used for the treatment of 28 cases of brucellosis, 6 of which failed to improve. Most of the reports summarized above fail to give either the dosage of serum employed or the exact method of its administration, or both, hence this information cannot be given here.

D'Oelsnitz and Liotard (37) reported on autoserum therapy in 1924. From 2 to 5 cc of serum, from a patient ill with undulant fever, were injected subcutaneously at the onset of a febrile period. Recoveries were obtained in 2 of 5 cases. Beattie and Rice (1) also described the successful treatment of 2 cases of brucellosis with an autogenous blood serum similarly prepared.

Our own experience has coincided with that of the above authors

We have observed the effects of only 2 types of serums, human convalescent serum and antiabortus-melitensis bovine serum. Two cases were treated with intramuscular injections of 50 cc of human serum and 200 cc of whole human blood, respectively, obtained from an individual who had recovered from undulant fever and who still had a serum titer of 1 to 320. Both became asymptomatic in approximately 2 weeks. Two other patients were injected intravenously with bovine serum, 1 of which became afebrile several days later and appeared to be cured. The second was not improved.

The reports on the use of antiserums are, in general, favorable, but the results are only temporary in most instances. Spectacular cures have not occurred, while disappointments were not infrequent. The temporary benefits are encouraging, and suggest that a concentrated serum might be more efficacious.

#### THErapy WITH TOXIC FILTRATES

Toxic filtrates, prepared from broth cultures of *Br abortus* and *Br melitensis*, have been used less extensively than serum or vaccine therapy in the treatment of the disease. Melitene and brucellin were most frequently employed. Burnet (38), in 1922, suggested the intradermal use of a sterile bouillon culture filtrate for the diagnosis of undulant fever. This was prepared by filtering a 1-month old broth culture of *Br melitensis* through a Chamberland L candle, and boiling it for 1 minute to decrease its toxicity. One-half of 1 per cent of phenol was added as a preservative. This material was called melitene.

Several men have used melitene therapeutically, injections of which resulted in the temporary exacerbation of symptoms for 24 hours, later followed by improvement. Debré, Marie and Giroud (39), in 1927, recommended weekly intradermal injections of 0.2 cc for therapeutic purposes. They noted that if a systemic reaction followed the injection, improvement occurred. In error, one patient was injected intramuscularly, which brought about increased fever and general discomfort, followed, also, by amelioration of symptoms. Lemierre, Marchal and Jaubert (40), in the same year, reported the successful treatment of one patient after 5 months of illness. She was injected intradermally with 0.1 cc of melitene, and became afebrile in 4 days, after a marked local and generalized reaction. She was observed for 5 months, during which time there was no recurrence.

Huddleson and Johnson (41), in 1933, described for the treatment of undulant fever a similar filtrate, called "brucellin," which they prepared from caprine, porcine, and bovine strains. They recommend 4 intramuscular injections, of from 1 to 5 cc, at 3-day intervals, after the patient has been tested intradermally with from 0.05 to 0.1 cc for sensitivity to the filtrate. The injections were followed by a 24-hour exacerbation of symptoms, followed by gradual defervescence during a week. The treatment and results were described on 12 patients, selected from a series of 80. One may doubt the diagnosis in some of these cases, for 18 failed to show bacteriological or serological evidence of the disease. They state, "Not all cases of long standing, that is, eight months or over, respond to treatment as readily as do those that are treated early."

Few investigators have used toxic filtrates, but it is evident that specific effects are not obtained. Favorable results are evidently dependent upon "shock." Possible harm from toxin should be considered before use. Our experience is limited to intradermal tests with brucellin, which frequently produce severe local reactions.

#### CHEMICAL THERAPY

Nineteen reports describe the use of chemicals for the treatment of 75 cases of undulant fever. Dyes, for the most part, have been employed, intravenously and by mouth, because of their supposed bactericidal effect. Use has been made of arsenical preparations, especially neosalvarsan and neoarsphenamine, which are believed to be toxic for members of the genus *Brucella*.

An interesting report on the treatment of 2 cases of undulant fever by the administration by mouth of capsules of methylene blue is that of Audibert and Rouslacroix (42), published in 1911. Each patient received 0.05 gram twice daily for 2 and 3 days, respectively, beginning 6 and 4 weeks after symptoms had developed. The latter became nauseated from the treatment and was unable to retain the dye. Hypodermic injections of 0.1 gram, therefore, were administered. The fever in each case gradually abated, and the patients were normal in 7 and 12 days after therapy was instituted.

Carpenter and Merriam (43), in 1926, used intravenous injections of a 1 per cent solution of mercurochrome on 2 patients who had been

ill with the disease in one case for 7 weeks and in the other for 4. In each instance the injection was followed shortly by chills and an elevation in the fever, which subsided to the pre-injection level within a day. Both patients made complete recoveries after a month. During the next 2 years, Gage and Gregory (44) Warren, Smith and Lindner (45), and Belyea (46), reported on 1 case each treated with mercurochrome injected intravenously. Belyea's case developed a marked systemic reaction, followed by chills, vomiting, and diarrhea. Each accredited recovery to the use of the dye.

Ross and Martin (47), in 1927, described their experiences with mercurochrome in 9 cases of brucellosis. Of 3 who received no other therapy, 1 recovered and 2 failed to improve. The remaining 6 cases received injections of heat-killed vaccine, prepared from strains of *Br abortus* and *Br melitensis*, in addition to mercurochrome. In some instances, the investigators injected 7 cc of a 2.5 per cent solution, which was frequently followed with a severe generalized reaction, albuminuria, and dysentery. They summarized their opinion by stating that the value of mercurochrome in undulant fever was not proven. Todd (48) subjected 2 patients to the same therapy and recorded them as cured after 24 hours, during which time there was a marked systemic response. Simpson and Bowers (49), in 1929, reported favorable results in 16 of 23 cases. In the following year Simpson (24) reported 6 failures from the intravenous use of mercurochrome.

Numerous reports on the intravenous use of acriflavine for the treatment of undulant fever have appeared. Simpson and Bowers (49) in 1929, stated that it was of doubtful benefit in "a few cases," while Simpson (24), one year later, reported no improvement in 5 cases so treated. Hoffman (50), in 1929, believed that the course of the disease in 2 cases was shortened by its intravenous use during the fourth week of illness. Three injections, varying from 0.1 to 0.4 gram, were given. They were followed by severe systemic responses. Giordano and Sensenich (51), in 1930, treated 2 cases intravenously with neutral acriflavine, with resulting violent reactions. One patient became afebrile in a few days, but experienced a recurrence of symptoms 8 months later, while treatment was discontinued in the second case because of severe reactions to each injection. Thurber (52), in the

same year, observed 5 of 7 cases injected intravenously with acriflavine to become asymptomatic within a month. In 2 other cases, improvement was noted. Beattie and Rice (1), in 1934, reported 6 cases treated by the same chemical. Five patients injected intravenously with either a 0.5 or a 1.0 per cent solution, became afebrile in from a week to a month. The sixth patient received the dye by mouth and evidently recovered. The average duration of illness in these 6 cases was 12 weeks.

Leavell, Poston and Amoss (53), in 1930, reported the treatment with methyl violet, given by mouth and by rectal enemas, of 2 patients with chronic brucellosis of porcine origin, after both had failed to improve following intravenous injections of mercurochrome. These patients were given by mouth daily, for 77 days, from 25 to 100 milligrams of methyl violet in capsules, as well as 300 cc enemas of either a 1 to 50,000 or a 1 to 100,000 aqueous solution of the same dye. A third case, infected with a bovine strain, which had suffered a recurrence of symptoms about one year after serum and vaccine therapy, was treated similarly with thionin. From 25 to 50 milligrams of the dye was given daily for 15 days, as well as 300 cc enemas of a 1 to 50,000 or a 1 to 100,000 aqueous solution of the same chemical. Previous to dye therapy, *Br. abortus* was isolated from the patients' stools, while subsequently, it was not cultivated. The therapy in these cases was based on Huddleson's demonstration that methyl violet exhibited a bacteriostatic action on porcine strains, while thionin was effective against cultures of bovine origin. Although this mode of treatment was instituted late in the disease, the authors ascribed to it the improvement that followed. Another patient, ill for 4 weeks with undulant fever, was given by the authors 50 milligrams of methyl violet in capsules by mouth daily for 14 days. Twice, at times separated by a 10 day interval, a 300 cc enema of a 1 to 5,000 solution of methyl violet was administered. *Br. abortus* was not isolated from the patient, making it impossible to determine the type of the infection. The course of the disease, however, was unaltered by the medication, and the patient was discharged, still febrile, to the care of her local physician.

A few cases have been treated with other chemicals. Simpson (24), in 1930, failed in the treatment of 2 cases with injections of neo-



arsphenamine Neosalvarsan was administered, intravenously, to 1 patient in our series, after receiving vaccine and serum treatment, as well as injections of mercury protiodide during 2 years' illness, following which no noticeable improvement occurred Fortney (54) used an intravenous injection of a 1 to 1,000 metaphen solution on a patient ill for 10 days with brucellosis The temperature became normal 6 days after treatment Colloidal metals have been employed, especially in France, with supposedly dramatic results Souleyre (55), in 1921, described the use of 5 cc doses of collargol intravenously, followed by an immediate marked febrile response, and then deferescence He also employed lantol, electrargol, and "collobiase" of gold, the intravenous injections of which usually resulted in "shock," after which symptoms of undulant fever gradually disappeared

Although bacteriostatic effects of dyes on *Br abortus* and *Br melitensis* have been demonstrated *in vitro*, this does not justify their clinical use For one thing it is usually impossible to inject sufficient amounts intravenously to obtain a concentration equal to that necessary to injure the infectious agent *in vitro* Furthermore, we have isolated *Br abortus* from guinea pigs injected with lethal doses of acriflavine and methyl violet (56)

The average duration of illness in the reported cases was not shortened, and in several instances, detrimental effects were noted after such therapy In the cases which appeared to recover as a result of chemical treatment, it will be noted that chills and fever, with an exacerbation of symptoms, occurred after the injection This reaction, we believe was responsible for the improvement

#### FOREIGN PROTEIN THERAPY

Because of the failure of vaccines, serums, and chemicals to cure protracted cases of undulant fever, many non-specific foreign proteins, designed to produce "shock," have been tried Vaccines prepared from cultures of *B typhosus*, *B paratyphosus A*, and *B paratyphosus B*, as used routinely for prophylactic vaccination, have been most extensively exploited intravenously, intramuscularly, and subcutaneously Kristensen (20), in 1928, mentions the use of typhoid vaccines for the treatment of undulant fever, and although no data on the number of cases were submitted, he evidently believed them to be of value

Budtz-Olsen (57), in 1930, reported on the treatment of 10 patients given intravenous typhoid vaccine. Four became afebrile after the first series of injections, while 2 recovered after a second series. The treatment was of questionable value in 2. There was a recurrence of symptoms in 1, following a remission, after the first series of injections, and a further case derived no benefit from the treatment. Simpson (24), in the same year, described the use of T A B vaccine on 8 cases. He stated, "As a general rule, those patients who experienced the most marked general reaction had a most favorable response to vaccine." Stage (58), in 1933, observed more satisfactory results in a series of 35 cases from the use of a typhoid vaccine than from Malta fever serum. Miller (59), in the same year, observed 7 patients subjected to intravenous therapy with T A B vaccine. Dramatic results occurred in 3 in which the first dose was succeeded by a marked systemic reaction, and the other 4 made satisfactory recoveries after several injections of the vaccine.

In our own series, 2 cases have received T A B vaccines intravenously. One patient, beginning in the sixth week of illness, was given 5 intravenous injections at 2-day intervals, beginning with doses of 10 million and terminating with 50 million organisms. Chills and fever occurred after each injection, following which the symptoms gradually disappeared and the patient was able to return to work in about 3.5 months. The vaccine occasioned no improvement in a second patient, ill for one year.

Injections of sterile milk were used by Ferro (60), in 1921, and by Awe and Palmer (61), in 1928. The former effected a cure in 5 weeks on 3 patients ill 2 months prior to therapy. From 2 to 3 intramuscular injections of 5 and 10 cc amounts were used. The latter investigators initiated the treatment in the sixth, tenth, and third weeks of illness. The temperatures of 2 of these patients became normal in 9 and 5 days, respectively. The third case was markedly improved. Simpson (24), 2 years later, reported that the injection of sterile milk had no effect on 4 cases.

Specially prepared bacterial proteins from *Br abortus* and *Br melitensis* have been employed therapeutically by several men, who considered them to be more antigenic and less toxic than the intact organisms. Cambéssedes and Garnier (62) used an abortus vaccine,

which they called "microbic proteins," prepared in a mortar by grinding cells that had been dried in vacuum, and resuspended in a physiological salt solution Schilling, Magee and Leitch (63) in 1931, obtained in 1 case a complete remission in 48 hours, after employing an "autogenous antigen" produced by alternately freezing and thawing a culture of *Br abortus* recovered from the patient Lemierre (64), in 1934, favored the use of a "microbic endoprotein" of *Br abortus* origin, extracted according to the Besredka method Severe "shock" usually followed intramuscular or subcutaneous injections of from 0.3 to 1.5 cc of the endoprotein, followed in a few days by remission

Attention has been directed above to our belief that "shock" rather than specific effects was responsible for any amelioration of symptoms The results of non-specific protein therapy, recorded in this section, support this contention

#### THERAPY WITH ARTIFICIALLY INDUCED FEVER

Izar and Moretti (65), in 1935, reported the recovery of 6 of 9 patients with undulant fever, after irradiation of the spleen and liver with short radio waves, from 4 to 8 meters in length The results in 2 instances were doubtful, while a third case did not improve The patients were subjected to from 60 to 25 "Sitzungen" Temperature charts presented in the report indicate that the treatments in some instances increased the fever The wave lengths mentioned above were employed because Izar and Famulari (66) had previously reported lethal effects on cultures of *Br abortus* from exposure to such wave lengths

Artificially induced fever has been employed by us in the treatment of 3 patients with chronic brucellosis One patient, moderately ill for two months, was subjected to a 3-hour fever of 39°C, produced by a high frequency oscillator, emitting waves 15 meters in length A 5-hour fever of 41.5°C was induced in two other patients by irradiation with carbon filament lamps The second patient had suffered for about a year from a low grade fever and general malaise, while a third had been ill for 3 months with the disease, including arthritis An apparent cure was effected in the first 2 cases, while the third was improved for approximately a year, after which the specific arthritis reappeared.

Although the number of cases treated with artificially induced fever is small, the favorable results support further the contention that a febrile reaction is an important factor in combating brucellosis. This is seen particularly in chronic cases, where the normal ability of the body to respond with an adequate fever to an infectious agent has become exhausted.

#### MIXED THERAPY

Many cases of undulant fever have been subjected to several types of therapy. The various combinations of chemicals, vaccines, and serums, in addition to symptomatic treatment, are too numerous to mention in detail.

It is to be expected that the more prolonged the illness, the greater the variety of therapeutic methods employed. When one type of treatment failed, another was instituted, to which the improvement or recovery was credited. When two or more types of therapy were used, a series of vaccine injections usually constituted one of them, which was either preceded or followed by some chemical. In many instances acutely ill patients received serum therapy first, then a vaccine was employed when the patient's condition permitted it. Several French investigators combined Brunet's melitene and either chemicals or vaccines for the treatment of chronic brucellosis.

The multitude and variety of therapeutic methods, as noted above, are striking evidence of their ineffectiveness. There is no evidence either that the combination of these agents accomplishes more than their use individually.

#### DISCUSSION

A successful treatment for undulant fever is still a matter for the future, for as yet no therapeutic agent has been found which has been proved to alter, to a significant extent, the natural course of the disease. A possible exception should be made to this statement in the instance of the protracted case, where various measures which induce a systemic reaction seem to bring about a remission. The literature on brucellosis which is concerned with modes of treatment is based on only a small percentage of the total number of cases which occurs annually. Thus, it is a surprise to learn that during the last quarter of a century

data are available on the treatment of fewer than 800 cases of brucellosis,—a comparatively small number, when at the present time 1,500 cases of the disease are diagnosed each year in the United States alone. In general, unsuccessful results are unpublished, and the available published information deals with the use, almost always on a small number of cases, of new remedies or therapeutic methods. Furthermore, specific measures are almost invariably instituted late in the disease and frequently when the course of the temperature shows clearly that convalescence has already begun. It is true, also, that the treatment of chronic brucellosis has received much more attention than that of the acute disease.

One of the significant facts revealed by a review of the literature is the close agreement which is found among the several authorities concerning the average duration of the disease. Thus, the average reported by 9 investigators is 11.3 weeks. Essentially this same period of illness is found in treated cases, regardless of the type of therapy employed, a fact which substantiates the statement made at the beginning of this discussion. (See table II.) The shortest average course of the disease, *i. e.*, 7.5 weeks, was secured by Corona in 8 cases treated with a lysed vaccine. It is significant, however, that he instituted treatment earlier than other investigators. The average of 12.5 weeks of illness for our own group of 26 cases treated symptomatically agrees closely with the period for 17 patients reported by Beattie and Rice (1), Awe and Palmer (61), and De la Chapelle (67). In Angle's (22) first communication on the therapeutic use of vaccine, 9 of 10 cases had illnesses totalling 117.5 weeks, or an average of 13 weeks per patient. Twelve cases treated by Huddleson (41) with brucellin, totalled 181 weeks of illness, making the average duration for each about 15 weeks. The 20 cases of Wherry, O'Neil and Foshay (35) that responded most favorably to serum suffered an average illness of 11 weeks. Similarly, the 6 chemically treated patients of Beattie and Rice (1) were sick for 12 weeks on the average.

After reviewing the publications on vaccine therapy, it is evident that a specific effect from its use is questionable. This conclusion is in accord with experimental work on animals, almost all of which has failed to demonstrate any curative value from injections of dead organisms. Indeed, it is quite usual following vaccine administration

to recover *Br abortus* or *Br melitensis* from naturally or artificially infected animals. Furthermore, the characteristic pathology of undulant fever, which resembles tuberculosis so closely, is such that, with our present knowledge at least, little value would be expected from vaccine.

No investigator has controlled his results on cases treated with some particular agent by making a comparison with a similar untreated group, or a group treated symptomatically only. Although the relatively low incidence of undulant fever makes such a controlled

TABLE II

*A correlation of therapeutic methods used for undulant fever with the average total duration of illness*

AUTHOR	YEAR	NUMBER OF CASES	AVERAGE DURATION OF ILLNESS	TREATMENT
			<i>weeks</i>	
Hughes	1897	372	10	Probably symptomatic
British Navy	1904	430	9.5	Probably symptomatic
Bassett Smith	1921	*	16	Various methods
Angel	1929	9	13	Vaccine
Hardy	1930	212	12	Various methods      Mostly symptomatic
Huddleson	1933	12	15	Brucellin
Beattie and Rice	1934	6	12	Acriflavine
Wherry, O'Neil and Foshay	1935	20	11	Antiserum (caprine)
Carpenter and Boak	1935	26	12.5	Symptomatic
Average			11.3	

\* Number not known, but based on a large experience

experiment difficult, the effort necessary to secure a series of alternately treated and untreated cases would be highly repaid.

Several students of brucellosis have emphasized the necessity of injecting vaccines in a way to produce "shock," having observed their best results after systemic reactions. It must be borne in mind, however, that the induction of "shock" is not without danger to the patient. Furthermore, we have observed several cases, treated with vaccine, which were made worse by its use. One patient, after receiving large doses, deteriorated mentally and finally died with extensive liver injury. The development of retrograde mental

changes from the toxic effects of vaccine must be considered seriously, before such treatment is given to a depressed case

It is worth while emphasizing that the benefits of fever depend on more than the simple injurious effects of the high temperature on the invading organisms. Corollary reactions, such as leucocytosis, accelerated phagocytosis, and increased antigen-antibody interaction occur. Furthermore, many other factors, not understood at present, are undoubtedly involved.

Although the relief of symptoms following serum therapy has usually been reported to be a temporary benefit only, this method of treatment may be advocated for acutely ill patients. Convalescent human serum is much less likely to produce an untoward reaction than are the various animal sera. Blood transfusion, particularly from an immune individual, is valuable in children and in cases with anemia. Recent reports on the successful use of hyperimmune animal sera of high agglutinin content give the hope that the method of serum therapy may be more successfully exploited in the future.

The employment of toxic filtrates, particularly brucellin, has attracted attention recently. A critical analysis of the reported cases, however, leads to a conservative view of their merit. Their administration leads to a febrile response, and often to a general exacerbation of symptoms. We believe that their favorable action is non-specific. The same may be said for chemotherapy.

A plea should be made for the prompt recognition and early treatment of undulant fever. On the other hand, failure to institute some special treatment early in the disease cannot be used as an excuse for its ineffectiveness. Moreover, recovery, which is usually spontaneous during the third month, must not be taken as proof of the efficacy of some therapeutic agent given at this time.

#### SUMMARY

A successful method for the treatment of brucellosis still awaits development, for as yet no therapeutic agent has been found which has been proved to alter, to a significant degree, the natural course of the disease. A noteworthy agreement that the average duration of the disease is 3 months is revealed by a survey of many reports. More striking still is the finding that this average period of illness prevails

in treated cases irrespective of the type of therapy employed. All of the therapeutic measures discussed in this review evoke a systemic reaction. We believe that it is this response, associated with increased fever and corollary phenomena, which is responsible for beneficial results rather than a specific reaction.

We wish to express our appreciation to Dr William S. McCann for making available to us the cases of undulant fever treated on the medical service. We wish to thank also Dr George Packer Berry for his interest in this review and for his help in its preparation.

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# ASPHYXIA AS A CONSEQUENCE OF NITROUS OXIDE ANESTHESIA

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WITH FOREWORD BY DR. YANDELL HENDERSON

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## FOREWORD

Asphyxia is one of the broadest and most important subjects in the entire range of the medical sciences.

Clinically asphyxia is the cause of death or serious damage in a wide variety of conditions ranging from pneumonia to carbon monoxide poisoning and asphyxia of the newborn.

Physiologically asphyxia is a disturbance of tissue respiration, which is the fundamental process of life. Knowledge gained through the study of asphyxia is thus a contribution to the basic problem of biology and medicine.

Pathologically asphyxia induces changes of structure in the brain and other organs that are probably of broader interest than those resulting from any other cause. The asphyxial degenerations of the tissues are, so to speak, the pathological base line from which all other tissue changes should be estimated.

The close relation of anesthesia and asphyxia is a subject of far



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## FOREWORD

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The close relation of anesthesia and asphyxia is a subject of far

reaching importance both practical and theoretical. This relation is nowhere so clearly shown as in nitrous oxide anesthesia, and in no previous work has the relation been so fully developed as in the accompanying monograph. It reveals that, aside from the well recognized and avoided hazard of the period of inhalation, nitrous oxide anesthesia involves a risk of such nervous and mental sequelae as those of prolonged carbon monoxide asphyxia.

To this risk surgeons and anesthetists must now give attention and no longer rest in the comforting conviction that nitrous oxide is the safest of all anesthetics. For short anesthetics it doubtless is. For long anesthetics the hazard of asphyxial sequelae is one that must hereafter be counted as a heavy weight tending to swing the balance against nitrous oxide anesthesia.

#### INTRODUCTION

The rôle played by asphyxia in the production of surgical anesthesia by anesthetic gases is as yet not entirely clear. The reason for this is due largely to lack of information as to the concentrations of oxygen, carbon dioxide and the gas in the blood before and after it has passed through the human brain. If our present conception is correct, unconsciousness is produced by the intrinsic narcotic action of the gas, reinforced to a variable extent by the accompanying anoxemia. With ethylene gas, this asphyxial element must be negligible since the amount of oxygen administered with it approaches the concentration in inspired air. On the other hand, the effect of nitrous oxide is predominantly an asphyxial one. Its untoward effects, especially the variable motor manifestations, have long been recognized by anesthetists and attributed by them to its asphyxial action. The relationship of serious delayed symptoms due to asphyxia of the cortical nerve cells has not been so fully appreciated. Since the so-called "anesthetic deaths" take place with dramatic suddenness while the patient is still under the effects of the anesthetic, nitrous oxide is frequently absolved of blame as the responsible lethal agent in these cases with delayed exitus.

The writer's interest in the asphyxial effect of nitrous oxide anesthesia was awakened when he was asked to see a comatose patient who presented generalized muscular twitchings and rigidity which

developed after a period of apnea while under this anesthetic. A study of the brain was made after a survival period of five days. The striking and characteristic changes in the nerve cells and the distribution of cortical necrosis suggested asphyxia as the cause of the symptoms. In the past five years thirteen such instances have been studied. In all of the nine cases terminating fatally autopsies were performed and a histologic study made of the tissues of the nervous system. The results of these clinical and pathologic studies form the basis of this report.

#### THE MODE OF ACTION OF NITROUS OXIDE

Nitrous oxide is a colorless gas with a characteristic odor and taste. It is capable of producing anesthesia rapidly by inhalation. Its non-explosiveness, the ease of induction of surgical anesthesia and the relative absence of residual discomfort have made it the anesthetic of choice in short operative procedures, particularly those of dentistry. Judged alone on the basis of fatalities at the time of operation, nitrous oxide has been considered one of the safest, if not the safest of anesthetic agents. It has been estimated that deaths from its use are less than one in five million. In the light of this study, however, it will be necessary to investigate anew this matter of its relative mortality and morbidity. A study into its mode of action, however, is first in order.

The essential problem of the physiologic action of nitrous oxide has been to determine to what extent its effects are due to its narcotic action on the one hand or to the accompanying anoxemia on the other.<sup>1</sup> In so far as body tissues in general are concerned, it has been found that nitrous oxide acts like any other indifferent gas which produces asphyxia by limiting the oxygen intake. Its effect on the brain, however, suggests that its action is not entirely asphyxial but is due in part to a specific narcotic action, perhaps dependent on its molecular form. Its action differs experimentally from other as-

<sup>1</sup> While the word "anoxemia" is not entirely accurate, since the term literally means *without oxygen* in the blood, it has become so well understood in its implications that it may be unwise to attempt to substitute any other designation for this condition. The term "hypoxemia" has been suggested in its stead (1). It is so obviously in error to say "cerebral anoxemia" that in this connection the more accurate term "cerebral anoxia" has been used to describe the effect of anoxemia on the brain.



phyxial gases in that the pulse is not so slow (inhibition center less capable of activity), convulsive movements are less marked (depressant action on motor nerve cells) and respiration ceases earlier (specific depressant action on the respiratory center) This specific depressant action is demonstrated when the gas is used even in a dilute mixture with oxygen (1.4) when characteristic narcotic effects are produced On the other hand, when diluted with nitrogen or air, these effects are not apparent Kemp (2) has shown that anesthesia produced by nitrous oxide immediately disappears when nitrogen is substituted for nitrous oxide. Sollman (3) concludes that its central action consists of a primary stimulation of the psychic areas, which are later depressed to insensibility.

It has long been suspected that the action of nitrous oxide was due in part at least to oxygen deficiency, based on earlier experiences when the gas was used without oxygen As early as 1899, in discussing death under nitrous oxide anesthesia, Hewitt (4) considered obstructive stertor, convulsive movements and cyanosis to be of anoxemic origin and not essential to the anesthesia of nitrous oxide This opinion has some basis in the experimental work of Bert (5) and Martin (6) who believed that in spite of a depressant effect of the gas on the respiratory center, death was actually due to a lack of oxygen Wieland (7) ascribed its action to an interference with oxidation processes in the central nervous system As a result of their estimations of oxygen, carbon dioxide and nitrous oxide concentrations in the blood of dogs under nitrous oxide anesthesia, Leake and Hertzmann (8) concluded that it was impossible to maintain surgical anesthesia without some degree of anoxemia This same conclusion was reached by Greene and his co-workers (9) who found a high concentration of nitrous oxide necessary for satisfactory surgical anesthesia in dogs This made it evident that some degree of anoxemia must always be present, and that the depth of the anesthesia depended not so much upon the concentration of nitrous oxide in the gas breathed as upon variations in the percentage of oxygen As the result of their experimental work on animals, Brown, Lucas and Henderson (10) stated that "patients anesthetized with nitrous oxide will always suffer from a severe degree of anoxemia and that this must impose a limitation on its use and increase its danger "

Macklin (11) arrived at the same conclusion from his clinical observations

On the basis of the evidence at hand, it seems evident, therefore, that varying degrees of anoxemia do exist and are necessary in the production of anesthesia with nitrous oxide and that cellular asphyxia strongly reinforces any direct narcotic action of the gas. As the higher concentrations of nitrous oxide are reached, there always exists the danger of irrecoverable damage to the brain. Should even a transient respiratory and circulatory failure occur under anesthesia, asphyxia of the cortical nerve cells occurs after the utilization of the small amount of available oxygen.

#### THE TOXICOLOGY OF NITROUS OXIDE

The undesirable manifestations of any anesthetic agent may be the result of its immediate effect, its inherent toxic properties or the production of undesirable physiologic states which it creates or due to secondary complications which it favors. With nitrous oxide, the toxic effects in so far as its narcotic action on the nerve centers is concerned, need be given little attention. This is shown by the fact that animals die about the same length of time after inhalation of nitrous oxide as after inert gases, such as hydrogen (12). If reliance can be placed on the report of Miller (13), it is evident that delayed effects may be due to circulatory and pulmonary complications. This observer found that such complications occurred more frequently after nitrous oxide than after ether anesthesia. Although this may be due in part at least to the fact that this agent is used in instances where ether is frankly dangerous, the unusually high incidence of cerebral vascular lesions (7-1) nevertheless suggests that some possible etiologic relationship does exist. The third possibility in the production of untoward effects, viz., the creation of undesirable physiologic states to such a degree that temporary or permanent serious injury results is of primary interest in this connection.

It has already been shown that the administration of nitrous oxide is accompanied by varying degrees of anoxemia and that the depth of the anesthesia is dependent more upon the reduction of oxygen than upon an increased concentration of nitrous oxide. It is to this state of anoxemia, advanced to a degree inconsistent with safety,

that we must turn for an explanation of a group of undesirable, serious and often lethal effects

*Anoxemia and nitrous oxide anesthesia* A number of classifications of anoxemia have been suggested based upon the etiologic factor producing it, the mechanism of its production or the acuteness with which it is produced. Barcroft (14) recognizes three forms of anoxemia, the *anoxic*, the *anemic* and *stagnant* types

The *anoxic type* is the most serious one. In this type the oxygen tension in the blood is lowered so that there is actually less oxygen in solution in the blood. To still further accentuate the difficulty the carbon dioxide tension is also lowered which decreases the rate of dissociation of oxyhemoglobin. Therefore, even the oxygen which is present in the blood is not readily available to the tissues. Anoxic anoxemia may result from a reduction of oxygen in inspired air by (experimental) substitution of inert gases (nitrogen), of a lowering of oxygen content of the air (high altitudes, rebreather), of an obstruction of the respiratory passages, of deficient aeration of the lungs (emphysema, collapse of the lungs), of a deficient absorption of oxygen through the alveolar walls (pneumonia), or finally it may be due to an inability to carry a sufficient quantity of oxygen in the blood (methemoglobin, in carbon monoxide poisoning).

In the *anemic type* the deficient amount of hemoglobin makes it impossible to carry the normal amount of oxygen, although the oxygen tension is normal. The amount of oxygen carried under such circumstances may still be sufficient to carry on tissue oxidation at rest or under limited activity.

The *stagnant type* of anoxemia is the result of a slowed circulation as that resulting from cardiac failure. The oxygen content and oxygen tension is practically normal under these circumstances, but the oxygen actually supplied to the tissues is reduced incidental to a slowing of the blood current.

In general anesthesia the phenomena observed closely resemble those of simple anoxemia. It is upon this resemblance that Verworn based his theory that anesthesia was indeed due to an interference with oxidation in the brain, with depression of cellular activity. Critical experimentation, however, seemed to show that this analogy could not be followed out to a finality and other theories as to the production of anesthesia have been looked upon with more favor. In recent years there has been some tendency to return to this theory to explain the production of anesthesia (Macklin (11)).

Whether or not asphyxia accounts for the anesthetic action of all general anesthetic agents, it has a peculiar and fitting application in the mode of

action of nitrous oxide In the administration of this gas, even when pure oxygen is given with it under pressure, the actual amount of available oxygen is reduced This results in a lowering of the oxygen tension in the blood and consequently reduces the amount available to the cerebral cells (anoxic anoxemia) The possibilities of mechanical difficulties in the apparatus and obstruction of the respiratory passages can further accentuate the degree of anoxemia already present

The delayed effects of asphyxia, particularly the peculiar nervous and mental symptoms have long been recognized It is not surprising, therefore, to observe such manifestations after anoxic states which accompany nitrous oxide anesthesia It is likely that the emphasis which has been placed on the immediate asphyxial effects observed with this anesthetic has largely obscured this second possibility

Anesthetists are cognizant of the transient cyanosis, stertor or respiratory irregularities which not infrequently occur in the use of nitrous oxide These manifestations are usually indicative of mild states of anoxemia, observed particularly when there is any mechanical interference with free breathing We are more concerned in this connection with the more serious effects of nitrous oxide asphyxia, namely (1) sudden death, (2) transient and recoverable cerebral symptoms, and (3) a group of residual and often characteristic manifestations which may ultimately result fatally While it is to this last group that attention is particularly directed, a brief discussion of the first two is in order

*Sudden death under nitrous oxide anesthesia* It has become customary to charge all deaths on the operating table to the anesthetic agent, and those occurring after removal of the patient to his bed to some other cause Both assumptions are fallacious In most instances of death on the operating table, the anesthetic is either merely the last straw or one of the closing incidents in the course of some progressively fatal lesion The difference between true anesthetic deaths and coincidental ones is illustrated in Miller's report (15) in which he refers to 11 cases with fatal outcome under nitrous oxide anesthesia, in only 2 of which death could be attributed to the gas This is also emphasized in Kaye's reports (16) of instances of death under nitrous oxide, in all of which some other lesion evidently responsible for the fatal issue was demonstrated at autopsy

An interesting aspect of this phase of the problem was presented

by Haveman (17) and Ramsey (18) in their reports on a large series of cases from Crotti's Clinic. Death during thyroidectomy or ligation of thyroid arteries or shortly thereafter was found to be due to acute cardiac dilatation or to acute thyrotoxicosis.

Those cases in which some serious terminal state existed, often the one for which the operation was being performed constituted, therefore, the majority of "anesthetic deaths." To further illustrate this point, table I is appended. It refers to a list of cases in which death occurred on the operating table under nitrous oxide anesthesia during a period of 7 years at the Los Angeles County General Hospital. The findings at the Coroner's autopsy are appended.

There is a second group of cases of sudden death under nitrous oxide anesthesia in which no apparent cause of death can be found. If available literature can be taken for a dependable criterion, they have become very rare in recent years. Reports were more frequent in the closing quarter of the last century. Death was attributed in such instance to a persistent thymus (Owen (19) and Davis (20)), to an individual idiosyncrasy to nitrous oxide (Adams (21)), or to pressure during the operation on the carotid sinus (Downs (22)). In view of the antemortem manifestations and the presence of vascular engorgement at autopsy, asphyxia may have been given this possibility as a possible cause of sudden death under nitrous oxide.

There is still a third group of cases of sudden death during nitrous oxide anesthesia. They are of rare occurrence and the explanation usually given is open to question. A few instances have been reported with some lesion affecting the respiratory passages. The case reported by Dent (23) had a submental abscess in which death was alleged to have been due to pressure of the abscess on the glottis. Respiratory failure in this case might have been due to pressure on the carotid sinus as Downs (22) has suggested. Cases with pulmonary lesions, such as tuberculosis, empyema or embolism of the pulmonary artery ought also to be included in this group, but these lesions and not the anesthetic may well be the cause of death. Attention will be drawn to the influence of pulmonary lesions in cerebral anoxia in a later section.

*Recoverable neurologic symptoms and signs with nitrous oxide anesthesia.* Well defined neurologic manifestations, often localizing in

TABLE I  
Sudden death on operating table under nitrous oxide anesthesia

NUM BER	AGE	SEX	CLINICAL DIAGNOSIS	OPERATION	DETAILS OF ANESTHESIA	AUTOPSY FINDINGS
1	46	F	Toxic adenoma of thyroid	Removal of adenoma	Difficulty with induction, took anesthetic poorly Sudden respiratory failure after 45 minutes	Upper respiratory passages small Enlargement of liver Distention of the stomach
2	50	M	Right nephrolithiasis	Nephrotomy	Either nitrous oxide Poor pre-operative condition Rapid fall in blood pressure	Partial coronary occlusion, fatty myocardium Stones left kidney, small abscesses right kidney
3	42	F	Acute appendicitis, peritonitis	Abdominal exploration	Poor pre-operative condition Rapid pulse, deep respirations, low blood pressure Respiratory failure after few minutes	Perforated gangrenous appendix with generalized peritonitis
4	27	M	Pulmonary tuberculosis	Thoracoplasty	Slight cyanosis from beginning Respirations labored Drop in blood pressure Sudden respiratory failure	Bilateral pulmonary tuberculosis Cavitation right lung, right pneumothorax Brain grossly normal
5	40	M	Urethral stricture with extravasation of urine	Cystotomy Multiple scrotal incisions	Poor pre-operative condition Falling blood pressure from start Respiratory embarrassment Sudden respiratory failure after 30 minutes	Mitral incompetence, enlargement of liver and spleen Urethra structure with extravasation of urine Brain grossly normal
6*	30	M	Cellulitis of neck following extraction of tooth	Incision of abscess	Poor pre-operative condition Respiratory failure for 8 minutes during anesthesia Respiratory failure again after 1 hour of anesthesia	Pontonsillar abscess with edema of the larynx Edema of tissues of the neck
7†	34	F	Ruptured ectopic pregnancy, intraabdominal hemorrhage, shock	Abdominal exploration	Poor pre-operative condition Gradual fall in blood pressure Cyanosis Irregular respirations Cardiorespiratory failure 30 minutes after discontinuing anesthesia	Ruptured ectopic pregnancy, right fallopian tube, intraabdominal hemorrhage
8	18	F	Pregnancy at term Possible cardiac disease	Forceps delivery, perineal repair	Either nitrous oxide for 55 minutes Respirations became feeble Only slight cyanosis Respiratory failure 5 minutes later	Pulmonary congestion Moderate dilatation of right heart Brain grossly normal

\* This case with pontonsillar abscess and laryngeal edema corresponds closely to some referred to in the literature A disturbed carotid sinus reflex might have been responsible for respiratory failure

† In the light of subsequent experience, if this patient had survived she would likely have had a serious cerebral defect It is similar to Case 10 in my series in that severe acute anemia was present and might have been a factor in favoring anoxemia

nature and transient in character, have been described as occurring during or after nitrous oxide anesthesia. These symptoms were even more common when an impure gas was inhaled for its exhilarating effects. The crude nitrous oxide gas, made by heating ammonium nitrate, at times gave rise to forcible and uncontrollable muscular movements. Stanley (24) described such an experience in 1842, the first reference to the subject the writer has been able to find.

In other instances the motor symptoms were more likely due to a coincident vascular lesion or to anoxemia itself than an impure gas. For example, Ashford (25) reported a case of hemiplegia following the use of nitrous oxide anesthesia for extraction of teeth. Warner (26) described jacksonian convulsions of the right extremities during gas anesthesia. Healy (27) reported convulsive seizures continuing for some days after administration of nitrous oxide for submental abscess. He also referred to other instances of minor or major convulsive seizures which he believed to be due to want of oxygen. In Green's case (28), wide-spread sensory and motor manifestations associated with aphasia were observed.

Evans (29) described several instances of convulsions occurring after nitrous oxide anesthesia. In one of his cases (Case 14), a 21 year old male remained comatose after an operation for reduction of a fracture. The pupils were dilated, the pulse rapid and respirations irregular. Convulsive movements were noted in the arms. He regained consciousness after administration of oxygen. The condition was attributed to suboxygenation, although its relation to the anoxic action of nitrous oxide was not considered.

Restriction of oxygen supply under nitrous oxide-oxygen anesthesia was also considered to be the cause of convulsions by Clement (30), who described three such instances. His first case, a 27 year old male, was operated upon for acute appendicitis under nitrous oxide and later ethylene anesthesia. On removal of the mask, the respirations became irregular and convulsions developed. He regained consciousness after an hour. In the second case, a seven year old child had several deciduous teeth removed under nitrous oxide-oxygen anesthesia. The child failed to regain consciousness and in a few minutes generalized convulsions made their appearance and continued for half an hour. The child recovered fully. In his third case, a four

year old child had several teeth removed under nitrous oxide anesthesia. Convulsions developed while under the anesthetic, but were controlled by the administration of oxygen. After removal of the anesthetic, the child failed to regain consciousness even after oxygen was given. Convulsions again occurred and persisted for half an hour. The child, mentally cloudy the remainder of the day, fully recovered the following day. The convulsive states in these cases were believed to be due to anoxemia. The author states that children were more susceptible to oxygen shortage than were adults.

Hewitt (31) has called attention to the peculiar tendency of alcoholics to have muscular spasms under nitrous oxide anesthesia, particularly if oxygen is not used. Rood and Webber (32) concurred in this and stated that it was also true of heavily built individuals. They believed that the occurrence of motor manifestations was evidence of the onset of asphyxia.

Buxton (33) noted the occurrence of ankle clonus in about one-third of the patients who were under nitrous oxide anesthesia for extraction of teeth. He also observed opisthotonos, emprosthotonos and rhythmic jactitations but did not believe them to be due to asphyxia. Horsley (34) found that under deep nitrous oxide anesthesia the superficial reflexes were usually abolished, while the deep reflexes (knee jerks) continued to be present.

It is evident from a study of this group of reported cases that minor cerebral symptoms, often localized in character may occur during the course of or shortly after nitrous oxide anesthesia. The significance of these localized manifestations will become more apparent in later sections.

*Serious residual cerebral manifestations* There remains a small group of cases whose more serious cerebral manifestations are also due to the anoxic effects of nitrous oxide. This type of case has been given but little attention in the literature, although no doubt many such cases have been observed, the clinical symptoms being attributed to other causes. Since no gross lesion of the brain is found at autopsy, the presence of a coincident or associated pulmonary lesion is apt to be emphasized as the cause of the patient's death.

This group of cases is characterized by the occurrence of a survival period of variable length in the fatal cases and by more or less per-



manent cerebral manifestations in those who survive. The first recorded cases that could be discovered were those of Caine (35), who reported three which seemed to answer the essential requirements. The first, a 39 year old female, was operated upon for gallbladder disease under nitrous oxide anesthesia. Respiratory failure occurred on the operating table. In spite of energetic artificial respiration, the patient remained in coma until the time of her death, about seventeen hours after induction of anesthesia. The second case, a 58 year old female, was operated upon for cholecystitis. A momentary respiratory and cardiac failure was treated by massage of the heart through the diaphragm. The patient was mentally hazy for four to six hours after the anesthetic. She complained of inability to use the left arm, but on examination the grip was found to be fairly strong (apraxia). Some residual visual impairment remained. A clinical diagnosis of edema of the brain was made by a consulting neurologist. The patient lost interest in her associates and surroundings and death occurred two months after a progressively downward course.

In the third case, a negro woman 37 years old was being operated upon for uterine fibroids when voluntary respiration suddenly ceased. Artificial respiration was administered for a period of five minutes before spontaneous breathing was restored. At the time of recovery, 3 hours later, she was found to be completely paralyzed and totally blind. She was unable to talk for 3 years and completely blind for 6 years. After 10 years she was able to distinguish visually only large objects, her speech was intelligible only to her immediate associates, and involuntary movements of the upper extremities were noted. The fourth patient observed by this author died on the operating table after all measures to combat the respiratory and cardiac failure had failed.

The author's conclusions in these cases are particularly interesting. He stated (1) that if the heart stops under nitrous oxide anesthesia with an insufficiency of oxygen, the chances for recovery are not good, (2) that restoration of cardiac and respiratory action does not necessarily indicate recovery of cerebral damage which may have occurred, (3) that residual symptoms may occur even after consciousness has been restored, and finally, (4) that the human brain is not as capable as that of the dog of withstanding a suspension of circulation for any great interval and returning to normal.

In Glynn's case (36) death occurred in a 17 year old male about 37 hours after nitrous oxide anesthesia for extraction of teeth. Respiratory failure during the anesthetic was combated successfully by resorting to artificial respiration. The patient remained drowsy and shortly after being put to bed developed generalized convulsions, which recurred every 15 minutes. Lumbar puncture revealed a clear, colorless cerebrospinal fluid under slightly increased pressure. The temperature became elevated before death. At autopsy the brain was congested and contained a few punctate hemorrhages. Aside from diminution of the tigroid substance in the nerve cell, no microscopic alterations were discovered. Death was attributed to the early pneumonic changes found in the bases of the lungs.

In a study already referred to, Evans (29) observed convulsive seizures after nitrous oxide anesthesia in a number of patients. In one instance (Case 4) the patient died in convulsions 14 hours after hysterectomy. No examination was made of the tissues of the nervous system.

A case reported by Yaskin (37) as non-suppurative encephalitis also seems to belong to this group. A patient, 23 years old, was delivered of a normal child under nitrous oxide anesthesia. She remained comatose for some days, presenting emotional outbursts at intervals. On one occasion she had an elevation of temperature and profuse perspiration. Dysarthria, dysphagia, limitation of extraocular movements and weakness of the lower left facial muscles were observed. Choreiform movements were present. There was, for a time, definite impairment of vision. The condition was thought to be due to anoxemia by Dr. William Spiller. The author considered nitrous oxide as a possible cause of the cerebral symptoms. The patient recovered after many months, and he believed the lesion to be predominantly in the white matter.

That peculiar mental states may also occur consequent to nitrous oxide anesthesia is evident from reports such as that of Savage (38). His patient became insane after administration of this anesthetic. Hewitt (31), one of the pioneers in the development of the use of nitrous oxide-oxygen anesthesia, summarizes the possibilities in his statement that

"Hysterical outbursts or transient states of hallucinations and struggling are sometimes met with. Protracted stupor, cataleptic states, hemiplegia

TABLE II

*Reported cases of anoxemia after nitrous oxide with fatal termination or serious cerebral symptoms*

AUTHOR	AGE	SEX	DIAGNOSIS	PRO-DROMATA	CARDIAC OR RESPIRATORY FAILURE	STAGE OF RE-ACTION	CEREBRAL MANIFESTATIONS	STAGE OF APPARENT RECOVERY	TERMINAL STAGE	OUTCOME SURVIVAL PERIOD
Savage (38)	Young adult	F	?	?	0	0	Delirium and incontinence Athetoid movements Delirious mania followed by dementia	0	0	Remained in a demented state
Caune (35) Case 1	39	F	Cholecystitis	?	Respiratory failure	0	Varying degrees of coma	After 7 hours	Rise T P R	Death in 17½ hours
Case 2	58	F	Cholecystitis	?	Cardiorespiratory failure	?	Mentally hazy parment Visual impairment Left apraxia	Conscious after 4-6 hours	Downward course	Death in 2 months
Case 3	37	F	Fibromyomata uteri	?	Respiratory failure	?	Residual paralysis and blindness Aphasia Athetoid and choreiform movements	After 3 hours	0	Alive after 10 years, blind, dysarthric and with athetosis
Glynn (36)	17	M	Extraction tooth	Cyanosis	Respiratory ? cardiac failure	Present	Convulsions	Lethargic	Rise in temperature	Died in 37 hours
Yaskin (37)	23	F	Pregnancy at term	0	0	0	Coma after anesthesia Emotional outbursts Dysarthria Impaired vision Choreiform movements	Conscious next day, apparent improvement for 3-4 days	0	Gradual recovery with residuals Myoclonic movements of tip of tongue

and even insanity have one and all followed the administration, but such sequelae are rare "

It is to this last group of cases that this study will give particular attention From a study of the following group of cases, characterized by the occurrence of residual neurologic manifestations after respiratory and cardiac failure under the anesthetic, it has been possible to establish a fairly well defined clinical syndrome which proves to be the result of characteristic cortical lesions of asphyxial origin <sup>2</sup>

# CASE REPORTS

*Case 1 Exploration for interlobar pulmonary abscess under nitrous oxide-oxygen anesthesia Period of irrationality, lethargy and aphasia with signs pointing to lesion of left frontal lobe Recovery Re-exploration two years later under nitrous oxide-oxygen anesthesia with marked cyanosis Generalized convulsions, continuous stupor and death Survival period 40 hours Autopsy*

A white man, 46 years old, was admitted to the Service of Thoracic Surgery of Dr Hans Schiffbauer at the Los Angeles County Hospital, on April 16, 1932, with a history of chronic cough, fatigue, pain in the right lower chest and loss of weight following an attack of pneumonia in 1928 A roentgenogram revealed a thin-walled cavity in the lower right lung in the vicinity of the interlobar fissure Repeated examinations of sputum disclosed no acid fast bacilli Wassermann and Kahn tests on the blood were negative Aside from a slight secondary anemia, the hemogram was normal

The first stage of an intrapleural exploration was performed without unusual incident on May 11, 1932 by Dr Schiffbauer under nitrous oxide-oxygen anesthesia The second stage of the operation was performed by the same surgeon on May 25, 1932, again under nitrous oxide-oxygen anesthesia The patient was cyanotic most of the time during anesthesia There were, however, no cardiac or respiratory irregularities The patient remained irrational and lethargic for a number of days after the operation,

<sup>2</sup> It should be borne in mind that the presence of a latent period is by no means indicative of cerebral anoxia, even when respiratory difficulties are noted under anesthesia A personally observed patient developed convulsions after failing to regain consciousness after anesthesia, during which a temporary respiratory failure occurred Autopsy revealed a cerebral embolism A case of cerebral hemorrhage after nitrous oxide anesthesia was reported by Wood (Brit Med J, 2 385, 1890) These experiences seem to agree with Miller's findings as to the relatively high incidence of cerebral vascular accidents under nitrous oxide anesthesia

and it was reported that he had muscular twitchings during this interval. He was examined a week after the operation by Dr. Delbert H. Werden of the Neurological staff, who found an increase in the deep reflexes, slightly more on the right, a bilateral ankle clonus and a right Babinski. Multiple metastatic abscesses were believed to be present; a major focus being suspected in the left frontal lobe. A few days later it was noticed that the patient used only one or two phrases which he repeated over and over again. He gradually recovered all of his mental faculties and it was assumed that he had had a toxic psychosis.

The wound in the thoracic wall was re-explored on August 2, 1933 under nitrous oxide-oxygen anesthesia without untoward manifestations.

On June 6, 1934 the wound was re-opened once more because the patient did not seem to be improving as he should. Nitrous oxide-oxygen anesthesia was again used. The patient was cyanotic throughout the period of the operation (45 minutes), but no failure of respiration or cardiac action occurred. About an hour after the operation, generalized convulsions made their appearance and grew progressively more frequent and severe until late in the evening, when they were practically continuous. They were controlled with sodium amytal (sodium isoamylethyl barbiturate). The patient remained in a state of deep coma.

He was examined the following day by the writer, who found him in deep coma from which he could not be aroused. The extremities were completely flaccid. Respiration was stertorous, the pulse rate was 160 per minute, and the rectal temperature was 104.4°. A bloody froth exuded from the nostrils. The head and eyes were deviated toward the left. The pupils were unequal, the left being larger than the right (adhesion of the iris to the cornea on the left). With the history of cyanosis under nitrous oxide followed by convulsions, a diagnosis of cerebral anoxia was made, although it was thought that the clinical picture was not entirely typical. The patient grew progressively worse with a steady rise in temperature (fig. 1), and died 40 hours after the operation.

An *autopsy* was performed by Dr. Hugh Edmondson, who brought the brain to the Cajal Laboratory for further study. A chronic abscess was found in the upper portion of the lower lobe of the right lung with several bronchial fistulae opening into it. There was an associated pulmonary edema and bronchopneumonia. There were no cardiac abnormalities or valvular lesions. The liver was enlarged (1580 grams) and on cut section, the center of the lobules had a yellow color. The kidneys were grossly normal. The brain weighed 1480 grams. There was marked congestion of the fine pial vessels. A few small subarachnoid hemorrhages were found.

over the dorsolateral surfaces of the cerebral hemispheres. The leptomeninges were thickened, particularly about the base. The convolutions were moderately flattened. There were no gross cortical abnormalities.

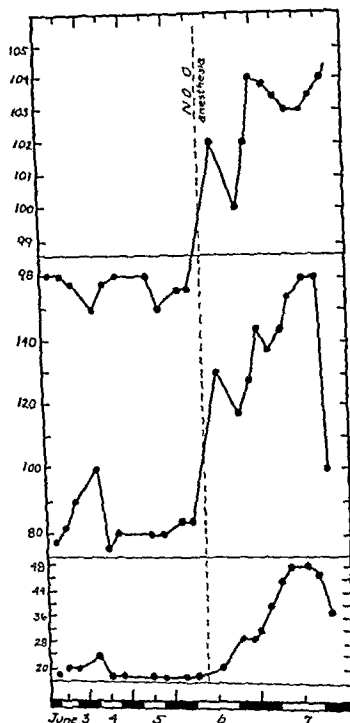


FIG. 1. CURVES OF TEMPERATURE, PULSE AND RESPIRATIONS IN CASE 1. Terminal drop in pulse and respirations suggest exhaustion of the centers.

On cut section a number of small areas of cortical softening were found, marked with petechial hemorrhages. Blocks of tissue were taken from the right and left precentral gyri, the right parietal lobe, the left visual cortex, the right and left lenticular nuclei, the upper medulla and cerebellar cortex.

Sections were stained or impregnated by the following methods: Hematoxylin and eosin, cyanin method for tigroid material, Penfield's combined method, and the neurofibrillar methods of Cajal and Bielschowsky.

*Histopathology* The arachnoid and the pia mater were thicker than usual and patches of local cellular proliferations were observed.

Typical zones of necrosis were observed in the sections from the mid-frontal, precentral and the parietal regions, most advanced and extensive

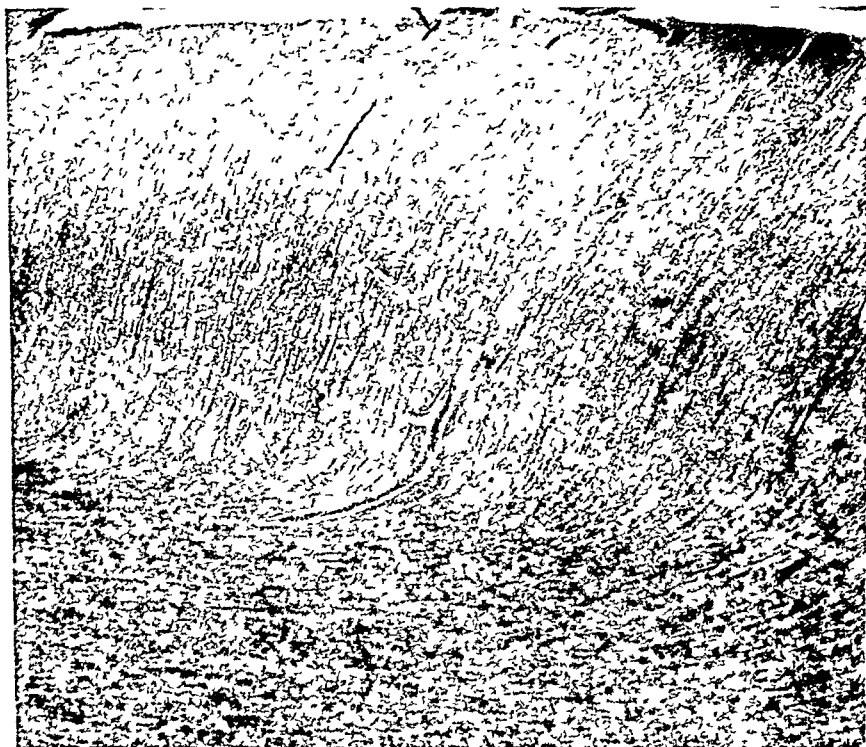


FIG. 2. NORMAL CORTEX SHOWN FOR COMPARISON WITH LATER FIGURES WHICH WILL DEMONSTRATE CORTICAL NECROSIS. REDUCED SILVER PREPARATION (CAJAL)  $\times 22$ .

in the frontal cortex. The deeper cortical layers were most profoundly affected, although the superficial and intermediate zones were also irregularly involved (fig. 3). The occipital lobes, the basal ganglia (particularly the lenticular nucleus) and the brain stem were free from any architectural or cellular alterations.

The nerve cells in the midfrontal cortex were severely damaged, almost universally so. They presented an irregular and ragged outline and most



FIG 3 CASE 1 SURVIVAL PERIOD 40 HOURS

*A*, right superior frontal convolution *B*, left upper precentral convolution In these sections the cortex was cut on the oblique *C*, relatively unaltered right parietal cortex *D*, cortex along left calcarine fissure (visual area) Reduced silver preparation  $\times 22$



of them appeared to be considerably shrunken. Their cytoplasm was stained a bright pink with eosin. They proved to be entirely devoid of tigroid material. In many of the cells a deposit of lipoidal pigment could be distinguished. Under higher magnifications these cells appeared coarsely granular. The neurofibrillar structure was universally fragmented and granular. In sections from the precentral gyrus and the parietal lobe, these changes were less marked and presented the characteristics of the so-called "sclerotic change." The pericellular spaces were enlarged and rounded. In the severely damaged areas the cortical nerve fibers were fragmented. Small endbulbs and varicosities were fairly numerous.

The microglia showed definite swelling of their cytoplasm either affecting all expansions symmetrically, or one or two polar ones predominantly. The oligodendroglia were acutely swollen in both the gray and white matter. The classic neuroglia showed no evidence of proliferation. In the necrotic areas the astrocytes were undergoing regressive changes.

The blood vessels were generally engorged, but there was no evidence of endothelial proliferation. The cells of Purkinje were but slightly altered and that not uniformly. The affected cells showed a minor loss of tigroid material, chiefly in the region of the apex of the cell. Herudiform degeneration (Cajal) was demonstrated in the reduced silver preparations.

*Comment* A number of very interesting features in the history of this patient should be stressed. He had been subjected to a number of thoracic operations under nitrous oxide-oxygen anesthesia. After the second anesthetic there was definite evidence of widespread cerebral involvement, the symptoms persisting for several weeks. Two years later the patient died 40 hours after nitrous oxide anesthesia. In the meantime, however, the same anesthetic was administered without untoward symptoms. This would seem to indicate that idiosyncrasy to the anesthetic agent played no part in the production of symptoms. It would be of interest to know the rôle played by deficient oxygenation of the blood incident to the extensive pulmonary lesion.

The first episode of cerebral manifestations, occurring two years before the patient's death, was evidently due to a transient anoxic state from which the patient fully recovered. The localizing signs pointed particularly to the left frontal lobe and an abscess was suspected in this situation. A careful search was made in sections of the left frontal lobe for evidences of an old lesion. No changes were

found grossly or microscopically which might so be interpreted. The absence of both gross cortical atrophy and advanced meningeal thickening in this region and the complete recovery of the patient would further indicate that the original anoxic changes were qualitative and recoverable. Since the frontal cortex was found to be most severely affected after the last exposure to nitrous oxide, it may be assumed that either the same regions tend to be affected in repeated episodes or that the first attack paves the way for damage done by the second.

Neurologic examination after the last anesthetic and shortly before death disclosed signs which suggested cerebral involvement of anoxic origin although they were not absolutely characteristic. At autopsy a number of small areas of softening were found which might have been due to small emboli. The brain of Case 6 showed similar areas of softening, although they were not described in detail by the pathologist performing the autopsy. In the cortical areas well distant from these focal lesions and in the corpus striatum the characteristic microscopic lesions of cerebral anoxia were found. This condition was probably responsible for the patient's death, although the pulmonary lesion may also have been a contributing factor.

*Case 2 Nitrous oxide-oxygen anesthesia for delivery and perineal repair. Respiratory failure under anesthetic. Generalized convulsions, muscular twitchings and deepening coma. Death after 43 hours. Autopsy.*

A Mexican primipara, 21 years old, was admitted at term to the Obstetrical Service of Dr. Edmund Lazard at the Los Angeles County Hospital on April 3, 1934. There had been some swelling of the ankles for a period of five months.

She was given pre-anesthetic medication of scopolamine gr  $\frac{1}{32}$  and sodium amytal (sodium isoamyl ethyl barbiturate) gr  $\frac{1}{2}$ , subcutaneously. Nitrous oxide-oxygen (90-10) was administered for a period of 4 minutes for an episiotomy. At the end of this period of anesthesia she was slightly cyanotic, but promptly recovered. She was given a few inhalations of the gas with each labor pain until delivery. After delivery of the placenta, nitrous oxide was again administered in order to repair the episiotomy wound. Because the patient was not completely anesthetized, ether was added (nitrous oxide 85 per cent, oxygen 15 per cent, ether  $\frac{1}{4}$ ). The percentage of nitrous oxide was later decreased (nitrous oxide 75 per cent, oxygen 25 per cent, ether  $\frac{1}{4}$ ) after anesthesia was established.

After half an hour of anesthesia the patient suddenly ceased to breathe. The heart rate at the moment was found to be regular and strong at 104 per minute. A carbon dioxide-oxygen mixture (10:90) was promptly administered together with artificial respiration. After a moment the patient took a deep breath followed by another period of apnea lasting about a minute. These alternations occurred for a period of six minutes, when spontaneous deep regular respirations were resumed. The blood pressure at this time was 122/90. The anesthetist stated that at no time during this interval was the patient cyanotic. Shortly thereafter generalized convulsions made their appearance and persisted with more or less intensity for several hours until finally controlled with sedatives.

The respiratory movements continued to be deep and labored. Muscular twitchings continued after the major convulsions had ceased. The muscles were universally spastic, and pathologic reflexes were found to be present.

Lumbar puncture revealed a clear, colorless fluid under decreased pressure. Albuminuria, not present before delivery, was now found to be present. Chemical examinations of the blood disclosed a non-protein nitrogen of 20 and 30 mgm per 100 cc on two consecutive occasions, and glucose 172 mgm per 100 cc. The carbon dioxide combining power was 40.1 volumes per cent the day following anesthesia and 39.8 volumes per cent the day of her death.

Neurologic examination revealed a conjugate deviation of the head and eyes to the left. The pupils were unequal, the right slightly larger than the left. The deep reflexes became very much depressed and pathologic reflexes could not be elicited. The generalized muscular spasticity and atypical Magnus-de Kleijn phenomena also disappeared. The temperature rose to 107° (fig. 4), and the patient died 43 hours after induction of anesthesia.

An autopsy was performed 15 hours postmortem by Dr. Cyril Francis. Bronchopneumonia was present in the lower lobes of both lungs. The cortex of both kidneys appeared thinner than usual. A hemorrhagic cystitis was also present. The uterus presented typical postpartum findings.

The superficial vessels of the brain were markedly engorged throughout. The convolutions were not flattened. The superficial layer of the cortex was yellowish in color and was universally softened in spite of excellent fixation of the remaining portions of the brain. In cross section the blood vessels of the white substance were found to be prominent. There were no gross alterations in the centrum or basal ganglia.

Blocks of tissue were taken from the cortex and subcortical white matter of the midfrontal and precentral gyri, the visual cortex, hippocampus, and lenticular nucleus of the left cerebral hemisphere. Blocks were also taken

through the medulla at the level of the inferior olivary nucleus and from the cerebellar cortex. They were stained or impregnated with series of methods utilized in cases previously studied.

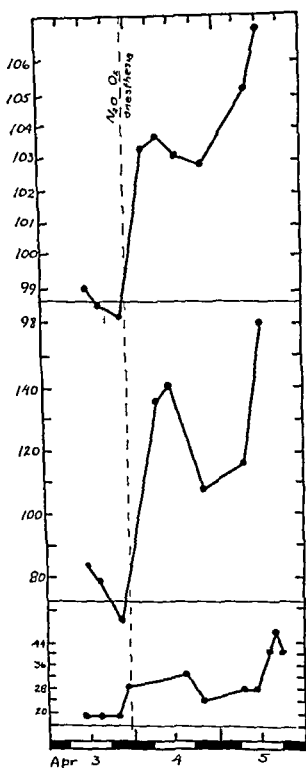


FIG. 4. CURVES OF TEMPERATURE, PULSE AND RESPIRATIONS IN CASE 2.

*Histopathology.* The arachnoid proved to be somewhat thicker than average, the increase being due to an apparent swelling of this membrane and not to cellular proliferation. About blood vessels in the pia mater,

however, local cellular proliferation was observed. These blood vessels were definitely engorged.



FIG 5 CASE 2 SURVIVAL PERIOD 43 HOURS SHOWING ZONAL NECROSIS OF THE DEEPER LAYERS AND PATCHY NECROSIS OF THE SUPERFICIAL LAYERS OF CORTEX

Dilatation of the perivascular spaces of cortex and edema of the subcortical white matter of the gyrus is also shown. Left visual area. Reduced silver preparations. Reduced from  $\times 22$ .

The superficial layers of the cerebral cortex were necrotic. The deeper layers of the cortex, adjacent to the white matter were found to be seriously injured universally (fig 5). The degeneration occurred as a single or

double zone of necrosis When traced along the cortex, the two necrotic zones were found to fuse into a broad zone at the apex of the gyrus The zone of smaller pyramidal cells was affected in an irregular fashion Some regions were extensively necrosed, while others escaped The zone between this and the superficial zone seemed to be the least affected As found in the previously studied cases, the degree of degeneration varied somewhat in the various regions studied, although serious damage was more universal

The cytoplasm of some of the pyramidal cells stained a brilliant pink color with eosin Structural changes in the nucleus were commonly observed Specific methods disclosed an absence of tigroid material A universal disintegration of the neurofibrillar apparatus was observed in reduced silver preparations, an atypical herudiform type of degeneration predominating The cortical nerve fibers revealed varicosities in their course and were usually fragmented

Preparations impregnated by the combined method revealed early swelling of the microglia, especially in the necrosed regions The oligodendroglia of the white matter were acutely swollen and early evidences of direct cell divisions were observed

In the lenticular nucleus a diffuse early softening of the gray matter was observed Some areas showed early necrosis The nerve cells showed the same types of change with specific methods as did those of the cerebral cortex The small blood vessels frequently disclosed small calcareous particles in their walls, either as a single rounded mass or as multiple globules

The cortex of the cerebellum was somewhat softened and fragmented The cells of Purkinje were the most seriously damaged elements Three types of change were observed (a) sclerotic change characterized by a shrinking of the cell and a dark homogeneous coloration of the cytoplasm, (b) ghost forms with general disintegration of the cell and (c) a less seriously damaged cell having a loss of most of the tigroid material Herudiform degeneration, fine and coarse granulation and fragmentation of the neurofibrils were also present

*Comment* An examination of the patient disclosed evidences of a typical state of cerebral anoxia With previous experiences in mind, the nitrous oxide was tested for impurities None were found to be present Since the same machine was used in two cases with similar clinical findings (see Case 12), attention was next directed to it as the possible source of trouble It was found that the valve controlling the percentage of oxygen and nitrous oxide permitted a most irregu-

lar admixture of these gases to flow into the bag. For example, when the indicator was set at 85% nitrous oxide and 15% oxygen, practically pure nitrous oxide was being delivered. The changing variability possibly accounted for the absence of an abrupt respirocardiac failure. The tendency to over-dosage of nitrous oxide throughout the period of anesthesia ultimately resulted in convulsions which signaled the cortical insult.

In this instance, we have an example of the last of the possibilities in the production of cerebral anoxia as a result of nitrous oxide anesthesia,—an imperfect mechanism for administration of the gases. A mechanically imperfect machine or one which has become so as a result of worn valves may be responsible. Where this possibility exists, checks on machines should be made at intervals to ascertain the percentage of each gas which is delivered at the indicated levels.

*Case 3 Convulsive seizures and coma following administration of nitrous oxide anesthesia for extraction of teeth. Death after two and a half days Autopsy*

A married man 42 years old, a painter, having generalized convulsions was admitted to the Cedars of Lebanon Hospital the afternoon of July 12, 1932. He had had eighteen teeth removed shortly before under nitrous oxide-oxygen anesthesia, which had lasted for half an hour. He failed to regain consciousness at the close of the anesthetic and shortly after developed generalized convulsions. He was attended by Dr. J. S. Snedaker, Jr.

On admission, the patient was found to be deeply comatose, respirations being of a stertorous character. Generalized convulsions occurred at intervals. The pupils were dilated, equal in size and reacted to light. Some divergence of the eyes was observed at times. The deep reflexes were universally spastic, slightly more marked on the left side. A bilateral Babinski was present.

The patient remained in a state of deep coma and repeated generalized convulsions were reported. The pulse rate was rapid and at times thready and weak. Respiration was of the Cheyne-Stokes type for a short period. The temperature fluctuated between 98 and 105 degrees (fig. 6). The blood pressure was normal and did not vary during the course of his illness. The coma seemed less deep on the second day, but convulsive seizures continued unabated. Examination by Dr. Carl W. Rand, who was called in consultation, revealed a typical decerebrate rigidity with extensor convulsions.

The blood glucose was found to be 146 mgm. and the non-protein nitrogen 44 mgm. per 100 cc. of blood. The white blood count was 19,500 per

cubic millimeter, 95 per cent of which were polynuclear cells. Repeated examinations of the urine showed increasing amounts of albumin. The spinal fluid was clear and was under no increase in pressure, a trace of globulin was present.

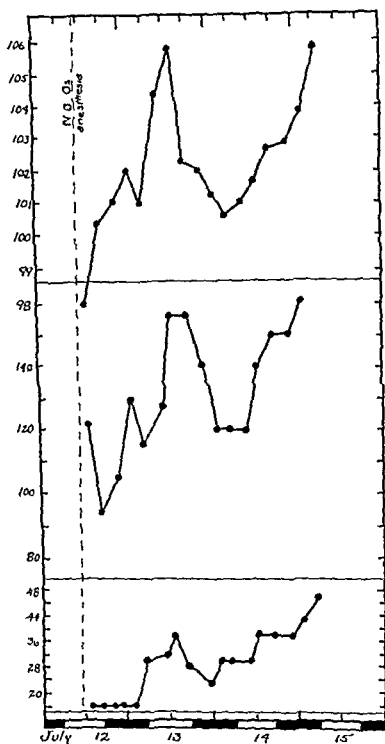


FIG. 6. CURVES OF TEMPERATURE, PULSE AND RESPIRATIONS IN CASE 3. PROGRESSIVE HYPERTHERMIA AFTER PRIMARY FALL IN TEMPERATURE.

The patient developed pulmonary edema, the temperature rose to 105.2, and death ensued about 64 hours after anesthesia.

An autopsy was performed by Dr. A. F. Wagner, Coroner's Surgeon,



who found no gross evidence of disease in any of the body organs. Tissue from the grossly normal brain was forwarded to the Cajal Neuropathology Laboratory for microscopic study. A number of blocks from various parts of the cerebral cortex, basal ganglia, brain stem and cerebellum were taken, which were stained or impregnated by the following methods: Hematoxylin and eosin, scharlach R, Penfield's combined method, Courville-Krajan method for myelin sheaths, cyanin method for nerve cells, the reduced silver (Cajal) and Bielschowsky's neurofibrillar method.

*Histopathology.* The arachnoid showed regional thickening but no cellular infiltration. Occasional phagocytes containing golden yellow pigment were observed.

The gray matter of the cerebrum and the cerebellum was found to be diffusely softer and more friable than normal, and was considerably broken up in the preparation. No characteristic foci of degeneration were observed in most of the cortical areas examined. In the lenticular nucleus, however, the necrotic areas were well defined and typical. The gray matter adjacent to the bundles of white fibers contained numerous vacuolar spaces. In the walls of the small and medium sized arteries of the corpus striatum were found small round calcareous particles.

The nerve cells were not universally injured, but here and there individual elements presented changes characteristic of either acute swelling ("ghost cells") or sclerotic change. The first type of change was characterized by swelling of the cell, loss of tigroid substance, vacuolization of the cytoplasm and degenerative changes in the nucleus. The sclerosed cells on the other hand were shrunken and distorted, presenting the typical cork-screw twists in the apical dendrite which could be traced for some distance in the interstitial tissues. Their cytoplasm was deeply and homogeneously stained a pinkish-purple color. At times the dark, shrunken and sometimes irregular nucleus could scarcely be made out. These changes were particularly marked in the lenticular nuclei and in the cerebellar cortex. The ganglion cells of the medulla (vagus nucleus) were but little altered.

The neurofibrillar structure was found to be altered more or less universally. In the cerebral cortex some of the cells proved to be entirely devoid of argentophilic material. Others showed typical granular degeneration. These changes were especially advanced in the Purkinje cells of the cerebellar cortex where fine and coarse granular, fusiform and herudiform degeneration was observed. Occasional small fusiform swellings were observed in the superficial fine transverse fibers of the cerebral cortex.

The blood vessels of the cortex and the lenticular nucleus frequently

showed thickening of their walls due to cellular proliferation. The lining endothelial cells were swollen and frequently vacuolated. Indentations and constrictions in the nuclear membrane indicated active direct cell division. Orange colored pigment was found to be present in the blood vessel walls, in phagocytic cells and in the perivascular spaces.

Well defined alterations in the interstitial cells were observed. In the vicinity of the small superficial cortical blood vessels mitotic figures were found in the microglia. With specific impregnation methods typical transitional forms of these cells were observed, particularly about the necrotic foci in the lenticular nucleus. Some pigmentation of these cells were observed. The cortical oligodendroglia were increased in number presenting a perineuronal satellitosis. They were acutely swollen in both the gray and white matter. Occasional instances of neuronophagia were observed. The oligodendroglia of the white matter were also increased in number.

*Comment.* In this instance the outstanding clinical manifestation was the almost constant generalized convulsions which occurred throughout the short survival period. The architectural changes in the cerebral cortex were minimal as compared to the typical foamy degeneration in the lenticular nuclei. The occurrence of calcareous deposits in the walls of the small blood vessels in the striatum is of special interest since similar findings are present after carbon monoxide poisoning.

*Case 4 Nitrous oxide oxygen anesthesia for biopsy of nodules in old scar at site of mastectomy. Cyanosis and cardio respiratory failure. Generalized convulsions. Death after three days. Autopsy.*

The patient, a housewife 50 years old, reported to her physician, Dr Wayland Morrison, when small nodules made their appearance in the axilla end along the scar of a former mastectomy wound. A carcinomatous left breast had been removed on August 11, 1933 under ethylene anesthesia.

On October 15, 1933, a resection of one of the nodules by biopsy was made under nitrous oxide oxygen anesthesia at the Glendale Sanitarium and Hospital. Shortly after the skin incision had been made the patient became cyanotic and suddenly ceased to breathe. Cardiac action had also apparently ceased, for the pulse could not be felt nor the heart beat detected with the stethoscope. Stimulants were promptly administered and artificial respiration begun. It was estimated that about five minutes elapsed before spontaneous respiration was re established and cardiac action restored.

On return to her room respiratory movements again became shallow for a short period. Generalized convulsions made their appearance shortly

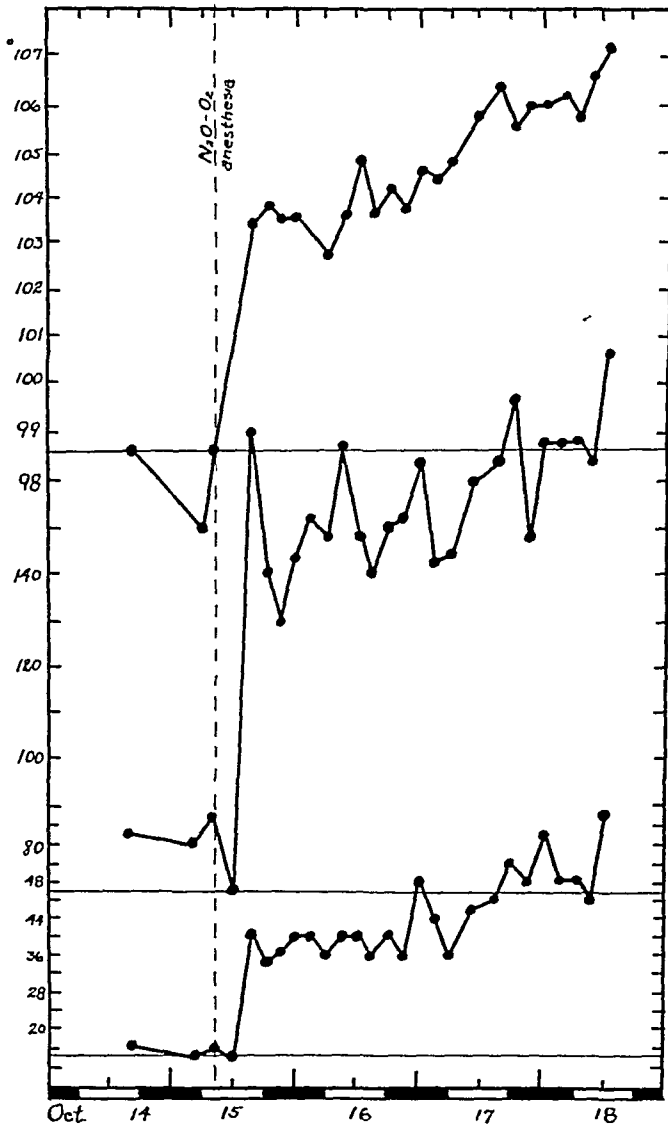


FIG 7 CURVES OF TEMPERATURE, PULSE AND RESPIRATIONS IN CASE 4 HIGH SUS TAINED CURVES AFTER ORIGINAL RISE

Marked respiratory irregularity was a prominent feature in this case

thereafter. The temperature ranged from 102 to 106° (fig 7) and the pulse rate became accelerated. At times the respirations were of Cheyne-Stokes variety, at times they were labored. Administration of oxygen

resulted in a marked slowing of the pulse. The patient died three days and five hours after respiratory failure during anesthesia.

The autopsy was performed by Dr. Orlyn B. Pratt. Suspecting that cerebral anoxemia was the cause of death, he courteously furnished the author with blocks of tissue from the cerebral cortex, corpus striatum, medulla and cerebellum for microscopic examination. The same series of stains and impregnation methods were employed as in Case 1. Sections from the liver showed congestion and fatty degeneration. A cloudy swelling of the kidneys was also found.

*Histopathology.* There was an irregular thickening of the arachnoid due to local patches of cellular proliferation. This membrane appeared to be adherent to the underlying pia mater in some situations. Granules of yellow pigment and globules of fat contained within macrophages were also observed.

The cerebral cortex was extremely friable and was marked with typical areas of foamy degeneration (fig. 8). Similar but not so characteristic areas were also found in the lenticular nucleus adjacent to bundles of white fibers. These areas were characterized by the presence of numerous vacuolar spaces in the interstitial tissues and enlargement of the perivascular and pericellular spaces.

Cellular alterations identical with those described in the first cases were also observed. Acute swelling and sclerotic change were commonly observed. In the first type the cell bodies were swollen, the cytoplasm being occupied by vacuolar spaces. The cell margin was often ragged. The nucleus also showed evidences of regressive change, such as disintegration of the chromatic substance and rupture of its membrane. In sclerotic change, the cell body was shrunken and distorted and the cytoplasm stained a homogeneous pinkish purple color. The nucleus was shrunken and irregular and was at times difficult to distinguish in the darkly colored cytoplasm. In cyanin preparations occasional cells showed a hyaline-like transformation of the cytoplasm. Tigroid granules could not be found in any of the cells. The neurofibrillar apparatus was found to be more or less extensively damaged in reduced silver preparations, while those impregnated according to Bielschowsky's technique showed alterations only in the vicinity of the areas of foamy degeneration. Most of the cells contained fat droplets in their cytoplasm (lipoidal degeneration). The cells of Purkinje presented a variable degree of regressive change characterized by granular necrosis of their neurofibrillae and loss of tigroid substance. The cortical nerve fibers showed considerable degenerative change. Fusiform swellings and endbulbs were not uncommonly observed.

The microglia had undergone variable degrees of transformation,

depending on their proximity to the areas of focal necrosis. Some of these cells contained mitotic figures. No fully developed compound granular corpuscles were observed. The oligodendroglia showed variable degrees of acute swelling and proliferation of these cells were taking place about the subcortical blood vessels. Neuronophagia was occasionally observed.

The small cortical blood vessels appeared engorged. Only minor early evidence of proliferation of the vascular endothelium was noted. Pigment and fat was found in their walls and in phagocytes in the perivascular spaces.



FIG 8 CASE 4 SURVIVAL PERIOD 3 HOURS

A, right middle frontal gyrus, B, left postcentral gyrus. Reduced silver preparation. Reduced from  $\times 22$ .

Argentophilic granules were also observed in the endothelial cells in reduced silver preparations.

*Comment* The onset of asphyxial symptoms within a few minutes after the induction of nitrous oxide anesthesia would suggest that, in some instances at least, these manifestations may be due to idiosyncrasy to nitrous oxide. The anesthetic agent being under complete control, scarcely enough time had elapsed after beginning of the

anesthesia for an extensive asphyxia of the brain to develop *per primum*. The cerebral damage presumably occurred during the interval of respirocardiac failure.

*Case 5 Respiratory failure under nitrous oxide-oxygen anesthesia for curettage of chronic osteomyelitic focus of right tibia. Residual coma and generalized muscular twitching with decerebrate rigidity. Death after four days and seven hours. Autopsy.*

A colored boy, six years old, was admitted to the Orthopedic Service of Alfred C. Gallant at the Los Angeles County General Hospital on Dec. 22, 1930 with multiple swellings and discharging foci of the skin of the trunk and extremities. Eight months before, he had "sprained" his right ankle and about a month later the skin ruptured at the point of injury and discharged pus. Two months before admission, multiple nodules appeared elsewhere over the trunk and extremities, some of which had also broken down and discharged pus. A history of progressive loss of weight, occasional night sweats and attacks of dyspnea and expectoration was also elicited.

The patient proved to be emaciated and apathetic. The cervical and inguinal lymph nodes were enlarged and discrete. The breath sounds were roughened over the apices of the lungs. The skin of the abdomen was marked with a number of small firm nodules. Larger firm subcutaneous nodules were palpable in the middorsal region of the back and over both arms and legs. A fluctuant swelling was present on the dorsum of the left hand and suppurating ulcers were observed on the back of the right thigh and about both ankles.

After observation for some weeks it was decided to drain the suppurative focus in the lower third of the bones of the right leg. This was done under nitrous oxide-oxygen anesthesia on February 10, 1931. About the time the operation was completed, the child suddenly stopped breathing and the pulse could not be felt. Stimulants were given and artificial respiration begun. The pulse again became perceptible in a few moments, but artificial respiration had to be continued for half an hour before spontaneous breathing was resumed. The respirations were short and shallow, tending to become deeper and slower in the course of the next six hours.

Within a few hours generalized hypertonicity of the body musculature developed, associated with muscular twitchings in the extremities, which at times assumed the proportions of true convulsive seizures. These movements were most marked in the upper extremities. A neurologic examination was made four hours after the respiratory crisis by Dr. Delbert Werden.

The child was found to be comatose, vomiting and perspiring freely. The pupils were equal and reacted well to light. The head and eyes were deviated to the left. Recurrent generalized convulsions were observed, the movement appearing first and being most marked in the right extremities. The deep reflexes were hyperactive throughout and pathologic reflexes were elicited on the left (the right leg was in a cast). A spinal puncture at the time revealed a clear colorless fluid under no increase in pressure. Examination of the urine showed an abundance of albumin and a trace of glucose (intravenous glucose had been given shortly before). There were 41 mgm of non-protein nitrogen per 100 cc of blood.

At intervals the child seemed to rouse himself, became restless and cried out. At these times the breathing became irregular and muscular twitchings made their appearance. Choreiform movements were also observed on occasion. The state of decerebrate rigidity became progressively more marked. The temperature became elevated (fig 9), the coma deepened and death ensued four days and seven hours after the episode of respiratory failure while under the anesthetic.

An *autopsy* was performed by Dr John H Schaefer, Coroner's Surgeon, who found a combined miliary and pneumonic tuberculous process in both lungs associated with dense pleural adhesions. The capsules of the liver and spleen were chronically thickened. Large tubercles were found in the spleen and in the cortex of the left kidney. The lesions of the bones of the right leg and of the skin were considered to be of tuberculous origin. The writer was graciously permitted to make a study of the brain. Blocks of tissue were taken from the superior frontal gyrus, precentral gyrus, the corpus striatum and the cerebellum. Sections were prepared in the same manner as in the previous cases.

*Histopathology* Only minor changes were observed in the leptomeninges, consisting of local areas of cellular proliferation. A collection of small globules of calcium in the walls of a large vein was a chance observation.

The architectural changes in the gray substance was somewhat advanced, over cases with a shorter survival period. In the areas of focal necrosis (fig 10) there was a marked increase in size of the perivascular and pericellular spaces and there were vacuole-like spaces in the interstitial tissues. These lesions were more common in the lenticular nuclei. The cerebral cortex was not affected to the same degree in all areas. Some sections revealed extensive superficial alteration, while in others only circumscribed pale areas were observed.

The pyramidal cells were found to be undergoing the characteristic types of degeneration, i e, acute swelling and a modified sclerotic change. The former type was manifested by swelling of the cytoplasm, loss of tigroid

material and vacuolization. The latter alteration was not entirely typical of advanced sclerotic change, in that the cytoplasm was not so deeply

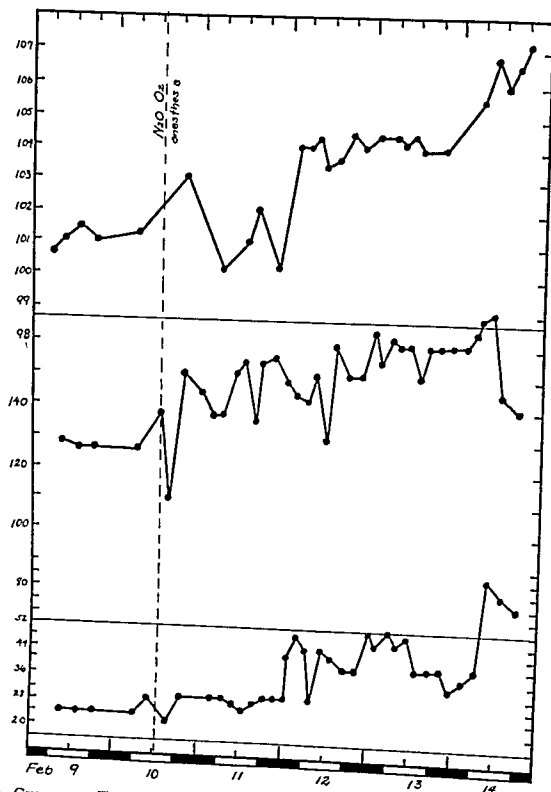


FIG 9 CURVES OF TEMPERATURE PULSE AND RESPIRATIONS IN CASE 5. TENDENCY TO SUSTAINED CURVES AFTER PRIMARY FALL NOTICED PARTICULARLY IN CURVE OF PULSE RATE

Note terminal fall in pulse and respirations

stained, and the apical dendrite failed to show so marked a degree of "corkscrew" twisting. The nerve cells were markedly shrunken and



distorted by the collection of fluid about them. All cells showed varying degrees of neurofibrillar degeneration. The large motor cells of the lenticular nucleus presented a homogeneous coagulated appearance. There was an almost universal occurrence of lipoidal deposit in the nerve cells of the brain.

Meriting particular mention were the alterations found in the cells of Purkinje. In routine preparations they were found to be markedly con-

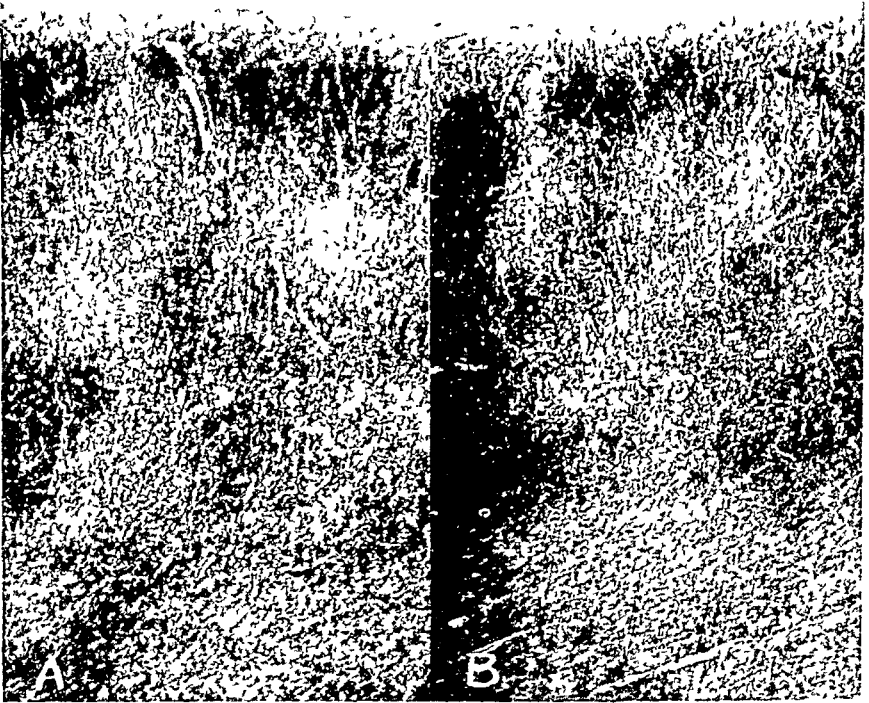


FIG. 10 CASE 5 SURVIVAL PERIOD 4 DAYS, 7 HOURS

*A*, dorsolateral and *B*, dorsomesial surface of left frontal lobe. Diffuse patchy necrosis of the cortex. Reduced silver preparations.  $\times 22$

tracted, stained a bright pink color and had a coarsely granular appearance. In contrast to the usual variable alterations of the neurofibrillar structure, there was a universal fine granular degeneration which gave the cytoplasm a "peppered" appearance. The cells were devoid of any trace of chromatic substance.

The oligodendroglia showed variable degrees of acute swelling in both the white and gray substance and early evidences of proliferation were present. Neuronophagia was occasionally observed, especially in the

corpus striatum Mitotic figures were found in the microglia of the basal ganglia, the cerebral and cerebellar cortex, and early transitional changes were present in these cells, as shown by the combined method

In certain areas of the cortex the blood vessels appeared to be increased in number Their walls were often thickened, due to active cellular proliferation, both by direct and mitotic cell division They proved to contain globules of fat and, at times, granules of argentophilic material The small vessels of the corpus striatum frequently contained small calcospheres

*Comment* The evident causative factors and the typical clinical picture made the finding of evidences of change in the brain a foregone conclusion The disturbances in respiration noted for several hours after anesthesia were suggestive of cerebral anoxia The existence of pulmonary tuberculosis may well have been a factor in precipitating the respiratory crisis by interfering with the oxygen—carbon dioxide exchange in the lungs The return of voluntary movements a few hours after anesthesia suggested a less marked degree of cortical damage This belief was confirmed by the finding of minor necrotic alterations in the cortex, even after a survival period of five days The occurrence of calcareous particles in the striatal blood vessels and the almost universal lipoidal pigmentation of nerve cells were of special interest in this case

*Case 6 Administration of nitrous oxide-oxygen supplementing spinal anesthesia for hysterectomy Continued coma Diffuse minor motor manifestations Survival period 5 days Autopsy*

A Caucasian housewife, 43 years old, was admitted to the Gynecological Service of Dr Lawrence Chaffin at the Los Angeles County General Hospital on January 17, 1931, with a diagnosis of fibrosis uteri and relaxed perineum The patient had complained of periods of irregular bleeding two or three times a month for the past eight years, which had resulted in a secondary anemia She had pulmonary tuberculosis with hemoptysis for a period of 18 months seven years before There had also been a nervous breakdown at some previous period Aside from the local pelvic disorder no unusual findings were recorded in the course of the examination Blood pressure was 126/80

A hysterectomy was performed on the morning of January 19, 1931, the operation having been started under spinal anesthesia When the effects of this anesthetic began to wear off one and a half hours later, nitrous oxide

oxygen was administered. Just as the abdomen was being closed ten minutes later the patient suddenly stopped breathing, the pulse became imperceptible and the blood pressure dropped to zero. After two minutes of artificial respiration normal respiratory movements were again started. Fifteen minutes later respirations again ceased when the table was raised from the Trendelenburg position. Artificial respiration was resorted to, and it was 12 minutes before voluntary gasping movements became manifest. The patient failed to regain consciousness, however, and consultation with members of the medical and neurological service was requested. The day following the operation an examination was made by the writer. The patient was found to be deeply comatose. All extremities were flaccid, although the deep reflexes were universally hyperactive, particularly in the right arm and the left leg. There was an equivocal bilateral Babinski and Chaddock and an unsustained left ankle clonus. The respiration and pulse were irregular. There was some difficulty in swallowing. The pupils were equal, regular and reacted sluggishly to light. There was a definite tendency to conjugate deviation of the head and eyes to the right. The possibility of multiple cerebral emboli was considered.

Repeated examination of the urine following the anesthetic revealed progressively increasing amounts of albumin and at times traces of glucose and acetone. Two days after the accident, chemical analysis revealed 137 mgm of sodium chloride per 100 cc of blood. On the day of the patient's death the spinal fluid was found to be under 250 mm of pressure and was clear and colorless.

The patient was examined repeatedly, varying diagnostic impressions being recorded. She gradually failed with steadily rising temperature and pulse rates (fig 11). She died January 24, 1931. An autopsy was performed one and a half hours postmortem by Dr. John L. Jackson, resident pathologist.

Small subpial hemorrhages were found over the surface of the brain along the course of the vessels, associated with a moderate degree of congestion. There seemed to be multiple small foci of softening throughout the cortex of the cerebral hemispheres, but there were no other gross changes. Several blocks of the cerebral cortex were removed for microscopic study. Antemortem clots were found in the branches of the pulmonary arteries towards the left base and right upper lobe, but there was no evidence of infarction. There were fatty changes in the liver.

Sections from the brain were prepared by the following methods: Hematoxylin and eosin, scharlach R for fat, cyanin method for tigroid material, the neurofibrillar methods of Cajal and Bielschowsky, the Courville-Krajan

method for myelin sheaths and Penfield's combined method for microglia and oligodendroglia

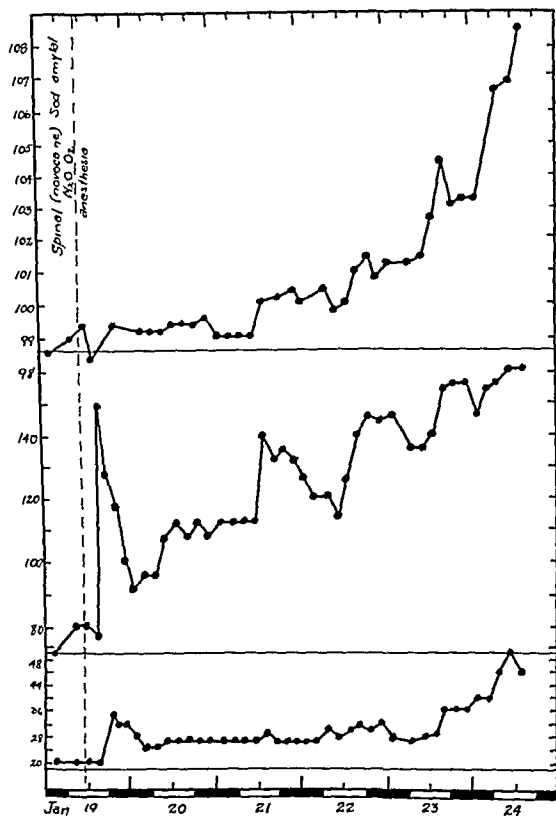


FIG 11 CURVES OF TEMPERATURE, PULSE AND RESPIRATIONS IN CASE 6 PROGRESSIVE RISE IN TEMPERATURE AFTER MINIMAL PRIMARY ELEVATION

*Histopathology* A slight irregular thickening of the arachnoid was noted but there was no evidence of cellular proliferation. Blocks of tissue

taken from the frontal cortex revealed patchy areas of necrosis affecting especially the superficial layers of the cortex, but often the deeper layers as well. Fusion of these patches were often observed, giving rise to irregular areas of degeneration (fig. 12).

Many of the nerve cells in the region of the "foamy" areas were undergoing regressive alteration either as acute disintegration (ghost cells) or sclerotic change. The former had lost all their tigroid material, their cytoplasm was vacuolated and the nuclei frequently fragmented. In the "sclerotic cells" there was a condensation of the chromatinic material in

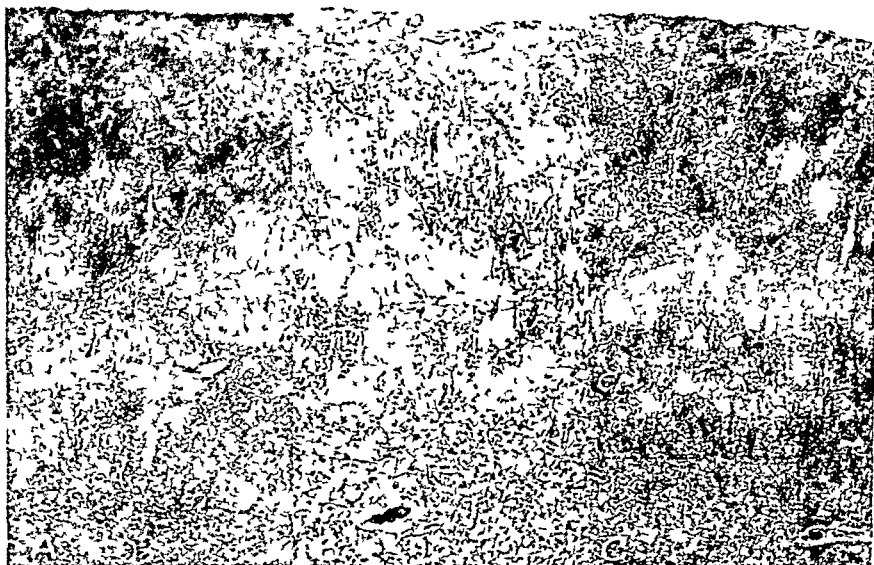


FIG. 12. CASE 6. SURVIVAL PERIOD 5 DAYS, 5 HOURS. LEFT MIDFRONTAL GYRUS. *A*, hematoxylin and eosin, *B*, Bielschowsky neurofibrillar method, and *C*, Cajal reduced silver preparation. All preparations from the same block. Reduced from  $\times 35$ . Irregular patchy necrosis is shown by all three methods.

the shrunken and distorted cell body, giving the cell a dark bluish purple color, in which the shrunken dark nucleus was often difficult to distinguish. The apical dendrite was often twisted and presented a wire-like distinctness. The other dendrites often presented peculiar mace-like swellings. The neurofibrillar apparatus was found to be degenerated, a change most marked about the nucleus. The smaller and more superficial pyramidal nerve cells were most seriously affected.

The small transverse fibers of the cortex revealed occasional rings and fusiform swellings. The large fibers entering the cortex also showed fusiform

enlargements, and some of their myelin sheaths also revealed characteristic globular swellings

No well-defined changes were observed in the blood vessels, excepting early evidences of direct cell division in the endothelial cells and the occurrence of orange colored pigment within their walls or within phagocytes in the perivascular spaces

The microglia about the foamy areas revealed early but characteristic transitional changes The oligodendroglia were acutely swollen Occasional instances of neuronophagia were observed

*Comment* This was the first of the series of cases here reported to come under the author's observation His own opinion was that multiple cerebral emboli were responsible for the cerebral manifestations Among the other possibilities considered by the numerous consultants were cerebral edema, novocaine and sodium amytal (sodium isoamylethyl barbiturate) poisoning In one of the bedside discussions a medical consultant (Dr Verne Mason) stated that anoxemia might be a cause for the condition, since respiratory failure for a considerable interval had occurred at the time of operation At that time the possible connection with the anesthetic agent, nitrous oxide, was not fully appreciated The occurrence of similar manifestations in other cases while under nitrous oxide anesthesia led to the more complete appreciation of the problems presented

*Case 7 Nitrous oxide oxygen-ether anesthesia for perineorrhaphy and repair after normal delivery Irregular respiratory movements without cyanosis during anesthesia Localized and generalized convulsions and coma Temporary improvement followed by decline and death Survival period 6½ days Autopsy*

A well developed and well nourished Mexican primipara 17 years old, was admitted in labor to the Obstetrical Service of Dr Edmund Lazard at the Los Angeles County Hospital on August 17, 1934 Subsequent history yielded the information that the patient had presented evidence of mental aberrations for a month prior to entrance to the hospital She was delivered of a normal male child 5 hours after admission

To facilitate delivery a perineorrhaphy was done by Dr George H Hewitt under nitrous oxide-oxygen anesthesia The patient recovered promptly from this anesthetic, although it was recalled later that she had appeared rather listless and indifferent to her surroundings and did not attempt to talk Nitrous oxide was again administered for repair of the

taken from the frontal cortex revealed patchy areas of necrosis affecting especially the superficial layers of the cortex, but often the deeper layers as well. Fusion of these patches were often observed, giving rise to irregular areas of degeneration (fig 12)

Many of the nerve cells in the region of the "foamy" areas were undergoing regressive alteration either as acute disintegration (ghost cells) or sclerotic change. The former had lost all their tigroid material, their cytoplasm was vacuolated and the nuclei frequently fragmented. In the "sclerotic cells" there was a condensation of the chromatinic material in



FIG 12 CASE 6 SURVIVAL PERIOD 5 DAYS, 5 HOURS LEFT MIDFRONTAL GYRUS. A, hematoxylin and eosin, B, Bielschowsky neurofibrillar method, and C, Cajal reduced silver preparation. All preparations from the same block. Reduced from  $\times 35$ . Irregular patchy necrosis is shown by all three methods.

the shrunken and distorted cell body, giving the cell a dark bluish color, in which the shrunken dark nucleus was often difficult to find. The apical dendrite was often twisted and presented a wire-like appearance. The other dendrites often presented peculiar mace-like swellings. The neurofibrillar apparatus was found to be degenerated, particularly marked about the nucleus. The nerve cells were most seriously affected.

The small transverse fibers of the nerve cells were most seriously affected. The large fibers

enlargements, and some of their myelin sheaths also revealed characteristic globular swellings

No well-defined changes were observed in the blood vessels, excepting early evidences of direct cell division in the endothelial cells and the occurrence of orange colored pigment within their walls or within phagocytes in the perivascular spaces

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*Comment* This was the first of the series of cases here reported to come under the author's observation. His own opinion was that multiple cerebral emboli were responsible for the cerebral manifestations. Among the other possibilities considered by the numerous consultants were cerebral edema, novocaine and sodium amytal (sodium isoamylethyl barbiturate) poisoning. In one of the bedside discussions a medical consultant (Dr. Verne Mason) stated that anoxemia might be a cause for the condition, since respiratory failure for a considerable interval had occurred at the time of operation. At that time the possible connection with the anesthetic agent, nitrous oxide, was not fully appreciated. The occurrence of similar manifestations in other cases while under nitrous oxide anesthesia led to the more complete appreciation of the problems presented.

*Case 7 Nitrous oxide-oxygen-ether anesthesia for perineorrhaphy and repair after normal delivery. Irregular respiratory movements without cyanosis during anesthesia. Localized and generalized convulsions and coma. Temporary improvement followed by decline and death. Survival period 6½ days. Autopsy.*

A well developed and well nourished Mexican primipara 17 years old, was admitted in labor to the Obstetrical Service of Dr. Edmund Lazard at the Los Angeles County Hospital on August 17, 1934. Subsequent history yielded the information that the patient had presented evidence of mental aberrations for a month prior to entrance to the hospital. She was delivered of a normal male child 5 hours after admission.

To facilitate delivery a perineorrhaphy was done by Dr. George H. Hewitt under nitrous oxide oxygen anesthesia. The patient recovered promptly from this anesthetic, although it was recalled later that she had appeared rather listless and indifferent to her surroundings and did not attempt to talk. Nitrous oxide was again administered for repair of the



perineum, ether being added after induction since the patient did not seem to be completely anesthetized. Toward the close of the operation, it was noticed that the respirations had become shallow and slowed. The expiratory phase in particular was definitely prolonged. There was no cyanosis at the time. The anesthetist examined the apparatus and failed to find any possible cause for the respiratory irregularity and the anesthetic was continued without interruption. A few moments later, several short periods of apnea were noted. Pure oxygen was promptly administered and normal breathing was promptly resumed, although the respirations were noticeably slowed. There was no cyanosis noted during this interval. A mixture of carbon dioxide and oxygen (90:10) was then administered for several minutes, but the slowed and somewhat shallow respirations were unaffected thereby.

Instead of regaining consciousness after the administration of the carbon dioxide-oxygen mixture, the patient remained deeply comatose. Two hours later, left side jacksonian seizures made their appearance. The convulsions soon became generalized. The patient remained in a semistuporous state and convulsive movements continued at short intervals for a period of 12 hours. The blood pressure which was 172/102 on entrance, continued to remain elevated.

The patient was examined two days later by Dr. J. M. Nielsen and the writer, who found the patient in a state of irritable coma, presenting episodes of involuntary laughing and crying. The deep reflexes were moderately increased and associated with a bilateral Babinski and Chaddock. The eyes were fixed in position of downward gaze. There were no signs of meningeal irritation.

She was re-examined the following day and although she was perhaps less deeply comatose than the day before, her condition was found to be essentially the same. The face was covered with perspiration. No attention was paid to spoken commands and patient did not seem to be able to see individuals or objects in the room. Outbursts of crying occurred whenever she was disturbed. No formed words or sentences were uttered. Voluntary movements were extremely limited in extent and all extremities were held in a position of slight flexion,—the forearms on the arms and the legs on the thighs. Only a suggestion of rigidity was noted, more in the upper extremities. The deep reflexes were slightly hyperactive throughout. A bilateral Hoffman, Babinski and Chaddock were still present.

The blood Wassermann and Kahn tests proved to be negative. Repeated urinalysis disclosed increasing amounts of albumin in the urine. The non-protein nitrogen was found to be 21 to 30 mgm per 100 cc of blood,

four and two days before death. Lumbar puncture revealed a clear colorless spinal fluid under more than 400 mm of water pressure. The

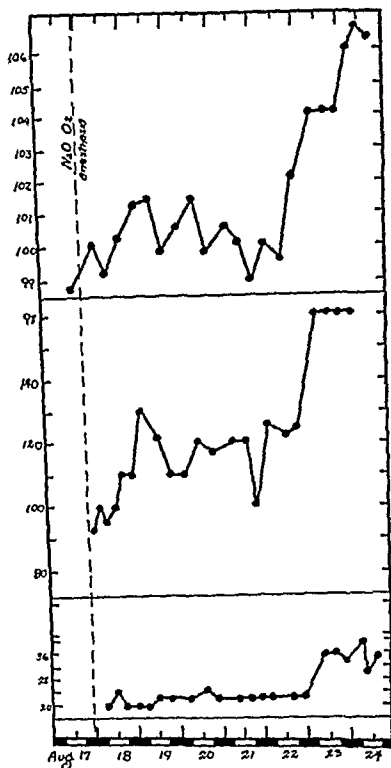


FIG 13 CURVES OF TEMPERATURE, PULSE AND RESPIRATIONS IN CASE 7 ABRUPT PRETERMINAL RISE AFTER PERIOD OF IRREGULAR LOW FEVER

fluid was cytologically and serologically negative. Blood studies on the day of death revealed 13,450 white cells per cubic millimeter.

The patient grew progressively worse after the first two days of apparent improvement. The coma deepened, the temperature became elevated

and the pulse and respiratory rates increased (fig 13) Throughout the survival period the blood pressure fluctuated between 170/130 and 125/95 Death occurred 6 days and 13 hours after administration of the anesthetic

An *autopsy* was performed 3 hours after death by Dr Hugh Edmondson, resident pathologist Petechial hemorrhages were found in the visceral pericardium and in the mucosa of the ureters The liver was enlarged (1620 grams) and somewhat swollen Its cut surface presented a mottled appearance The cortex of the kidneys was also somewhat swollen

The pia mater presented a marked congestion of the small blood vessels and the larger veins were full and somewhat tortuous The convolutions were not particularly flattened There were several spots of subarachnoid hemorrhage about the size of a dime over the dorsolateral surfaces of the cerebral hemispheres After prolonged fixation, it was noted that the cortex of the brain was still very friable and easily injured On cross section it appeared to have a faint yellow color, particularly in the region of the calcarine fissure

In order to obtain a more accurate conception of the extent and degree of degeneration than was obtained in a study of the previous cases, blocks of tissue were taken from symmetrical positions in functionally important areas in the cerebral hemispheres and from the brain stem and cerebellum This was done in order to make comparisons as to extent and severity of degeneration on either side The areas studied were the midfrontal convolutions, the body and tail of the caudate nucleus, the thalamus, the frontal operculi, the hippocampi, the central regions (arm area), anterior transverse temporal gyri (auditory area), visual cortex about the calcarine fissure (visual cortex), midbrain at the level of the red nucleus, the caudal pons (level of the nucleus of the vagus) and symmetrical areas in the cerebellar lobes

The findings in the stained and impregnated sections were characteristic of cerebral anoxia but showed even a more advanced state of necrosis in some areas than was observed in Case 6, as would be expected from the longer survival period

The meninges showed accumulations of cells scattered here and there, indicative of active proliferation The pial blood vessels were engorged Lymphocytes were scattered throughout the meninges but were most numerous in the vicinity of the blood vessels At times small circumscribed clusters of these cells were observed No calcareous particles were found

The cortex commonly showed various degrees of necrosis in the numerous sections Corresponding areas from the cortex of the cerebral hemispheres as a rule did not show the same degree of injury, nor was one hemisphere predominantly affected This seemed to confirm the impression gained

from a study of previous cases that the cortex was not uniformly damaged. The accompanying illustration (fig 14) shows the type of necrosis found in the various blocks most seriously affected. In the involved areas typical alterations in the cortical architecture and cellular elements were observed—early proliferation of the subependymal astrocytes, patchy necrosis, dilated pericellular and perivascular spaces, engorgement of the blood

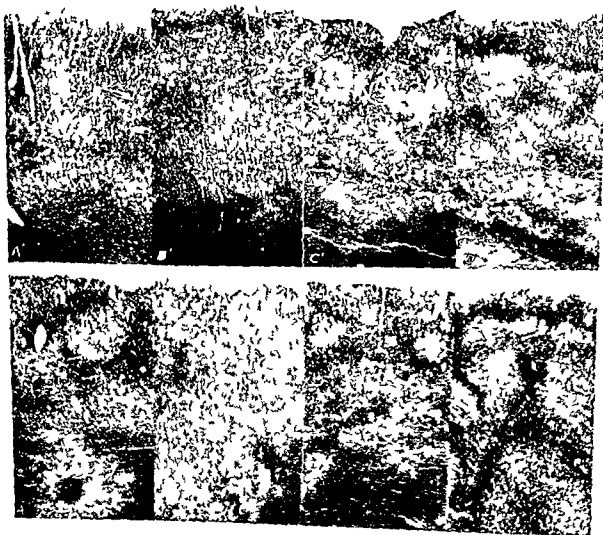


FIG 14 CASE 7 SURVIVAL PERIOD 6 DAYS 13 HOURS

*A, B, right and left middle frontal convolutions, C, D, right and left precentral convolutions (arm areas), E, F, right and left occipital areas. The various types of necrosis is illustrated in these sections, i.e. zone of necrosis and circumscribed and diffuse patchy necrosis. Note patch of necrosis about lateral branch of cortical vessel in C. Numerous other blocks showed little or no cortical degeneration. All reduced silver preparation. Reduced from X22.*

vessels, new formation of blood vessels, perivascular round cell infiltration, sclerosis and acute swelling of the nerve cells and beginning proliferation of the interstitial cells as manifested by the numerous mitotic figures. In the occipital lobes, where the cortical damage was most advanced routine staining methods disclosed marked pyknosis of the nuclei of the interstitial cells.

Perhaps the most interesting feature

shown in previous cases, was the new formation of blood vessels. The smaller vessels were definitely increased in numbers, and in the larger vessels the cellular elements had become markedly proliferated. Mitotic figures were commonly observed. This development of new vessels was not uniform in all areas nor in all parts of any one section. It was not unusual to find a large number of small vessels within a circumscribed area while the surrounding region appeared quite normal in this respect. In the areas of extensive necrosis the process seemed limited to the margin of the affected cortex. In the sections showing less architectural change, the process was more advanced, probably because destruction was less marked.

There was at times a zone of edema of varying width in the subjacent white matter in sections showing a seriously damaged cortex. The subcortical blood vessels were definitely engorged. The oligodendroglia were acutely swollen and showed early evidence of proliferation.

The cells of the corpus striatum and the thalamus were devoid of any gross changes and areas of necrosis and proliferation of blood vessels were not found. No calcareous particles were present in the walls of the small blood vessels, such as were found in some of the previous cases.

The nerve cells of the midbrain and pons showed no appreciable change. The cells of Purkinje showed variable degrees of loss of their tigroid material and degeneration of their neurofibrillar apparatus.

*Comment.* There are a number of features in this case which should be emphasized. In the first place, a severe and ultimately fatal insult to the cerebral cortex was sustained during nitrous oxide anesthesia without evidence of cyanosis. While it had been recognized for some time that cyanosis and anoxemia are not synonymous and do not necessarily accompany each other, some clinicians still cling to this notion. The appearance of recovery in the first few days with subsequent decline corresponds to the short transient period of recovery observed in the patients with shorter survival periods. The convulsive seizures and continued elevation of blood pressure suggested a toxic state associated with pregnancy. There were, however, no physical evidences of toxemia. From a pathologic standpoint the demonstration of the irregularity and the diffuseness of the cortical necrosis was of special interest and significance. There was no necrosis in the corpus striatum, a variation not observed in other cases.

*Case 8 Respiratory irregularities under nitrous oxide-oxygen anesthesia for curettage of the uterus Coma followed by delirium Septicemia Death 19 days later Autopsy*

A Caucasian housewife 35 years old was admitted to the Obstetrical Service of Dr Edmund Lazard at the Los Angeles County Hospital on February 12, 1931 with the diagnosis of incomplete abortion. A curettage of the uterus was performed in the afternoon of February 14th under nitrous oxide-oxygen anesthesia. The anesthetic was taken poorly from the outset, the respirations being very deep and irregular. In spite of withdrawal of the anesthetic and the prompt administration of a carbon dioxide-oxygen (10:90) mixture, respirations continued to be of a "forced" character and the interval between them was prolonged. Twelve minutes after the time the anesthetic had been started the patient suddenly stopped breathing, the pupils dilated and the pulse became very rapid and weak. After vigorous stimulation and artificial respiration, spontaneous respiration of a "gasping" character was resumed after two minutes. The patient remained unconscious, however, and twitching movements of the tongue and jaw were observed.

The patient was examined by the writer before she was removed from the operating room. She was deeply comatose, voluntary movements being limited to minor purposeless motions of the hands. The pupils were small and equal. The eyes were deviated upward and slightly outward. There was an active perspiration about the mouth and neck, a circumoral pallor was present, while the cheeks were flushed. The deep reflexes were present, active and equal, associated with a bilateral ankle clonus and a bilateral Babinski, Chaddock and Oppenheim. The corneal and abdominal reflexes were absent. A peculiar movement of the tongue was observed, characterized by fine fibrillary twitchings of its tip at the beginning of periods of hyperpnea followed by coarse up and down movements of its midportion posteriorly, as respirations became deeper. These movements were not present during the periods of apnea.

Within a few hours the patient became restless. At intervals the jaw was tightly closed, associated with periods of generalized body rigidity. This was followed by active delirium with increased motor activity and screaming at frequent intervals. Retching and occasional vomiting occurred. Visual hallucinations and delusions were evidently present during the period of excitement. The patient was transferred to the psychopathic ward. She continued to have periods of acute mania and complete restraint was necessary. The temperature curve showed daily variations between 99.8 and 104°, and at times toward the end, of 105°. Blood culture demon-

strated the presence of pneumococci. Before death muscular twitchings made their appearance, developing progressively into a marked constant tremor. Death occurred on March 5, 1931.

An *autopsy* was performed by Dr. Lawrence Parsons, pathologist, 15 hours after death. Several thrombi were found in the pulmonary arteries of the left lower lobe together with some hypostatic congestion. There was an extensive thrombosis of the right external iliac and femoral veins. A small necrotic area was found in the posterior wall of the fundus uteri associated with a thrombosis of the veins in the left broad ligament. The brain was grossly normal. Microscopically, there was a severe cloudy swelling of the kidneys and the spleen revealed bacterial foci containing pneumococci.

*Histopathology* Sections from the cerebral cortex were prepared with the same methods as in the previous cases. The arachnoid revealed only a minor diffuse thickening. There were no gross areas of necrosis as were found in the cases with a short survival period. Occasional scattered cells revealed the alterations previously characterized as acute swelling or sclerosis. Such cells revealed neurofibrillar degeneration and disintegration of the chromatic material. The oligodendroglia were acutely swollen, while the microglia revealed no change. In the perivascular spaces were found macrophages loaded with yellow pigment.

*Comment* This case is one of unusual interest, in that a minor and probably recoverable state of cerebral anoxia occurred during nitrous oxide-oxygen anesthesia. The patient's death was ultimately due to a pneumococcic septicemia. In the sections studied only occasional scattered cells showed evidence of change, but these changes were similar to those found in the previous cases. Unfortunately, a more critical study was not done, owing to the limited amount of material obtained at autopsy. If the transient anoxic state was responsible for the changes in the nerve cells observed in the sections from the brain, these findings probably represent the cerebral alterations in patients who recover from the condition. When discovered, such cases should be followed clinically to determine whether or not residual neurologic or psychiatric manifestations persist.

*Case 9* *Extraction of teeth under nitrous oxide-oxygen anesthesia. Transient respiratory failure followed by convulsions and coma for 24 hours. Improvement in mental status for several days. Complete blindness followed by deep coma and death in 26 days after onset. Autopsy.*

A white man 27 years old suddenly developed respiratory failure after 40 minutes of nitrous oxide-oxygen anesthesia, during which several teeth had been extracted. His past history, aside from periodic alcoholism, was essentially negative. The pulse was imperceptible during the period of apnea. Spontaneous respiration was resumed after vigorous measures of resuscitation had been instituted.

He was seen by Dr. Louis B. Baldwin, a medical consultant, one and a half hour later, who found the patient to be deeply comatose with jerky shallow respirations. The deep reflexes were universally hyperactive and a bilateral Babinski and left ankle clonus were present. Peculiar convulsive phenomena of short duration were observed. The pulse would at times suddenly become more rapid. During these episodes there was a marked rigidity of the neck with opisthotonos, marked dilatation of the pupils and a slow lateral nystagmus of short duration. During this attack, various muscle groups would become more rigid with a tendency to lateralize to the extremities of either one side or the other. There was noticed a twitching of the thumb and forefinger of the left hand for 5 to 10 minutes at a time. The hands frequently assumed a typical carpopedal position during the convulsive attacks.

After a period of deep coma lasting 24 hours, the patient became restless and irrational. The speech was slow and hesitant, but the words were clearly enunciated. A conjugate deviation of the eyes to the right, which persisted for several days, was noted. The deep reflexes were active and equal on both sides, though decreased in the upper extremities. A bilateral Babinski was still present. The patient remained in a confused mental state and speech was slurred. Although he made no complaint of blurred vision, he was just able to distinguish nearby objects. In the course of a few days a weakness of both lower and upper extremities was noted, most marked in the right arm.

Three days after onset the patient seemed more rational, but was extremely restless. He was conscious of the frequent violent and aimless movements but was entirely unable to control them. He stated that his vision was perfectly normal and the weakness in the right arm was less marked. The following day the patient seemed clear and cooperative, although the purposeless movements persisted. Visual fields were found to be normal to rough test. The weakness and incoordination of the right upper extremity and the bilateral Babinski persisted. The patient complained of a feeling that the right hand was swollen. The next day the patient again became stuporous and when aroused was not able to recognize individuals and said that he was completely blind.



Lumbar puncture revealed a perfectly clear fluid clinically and serologically normal. The blood count and urinalysis were also normal.

During the remaining days of life the patient was irrational or comatose, and was entirely oblivious of his surroundings. The temperature curve was irregular (fig 15), and the patient perspired freely. The heart was

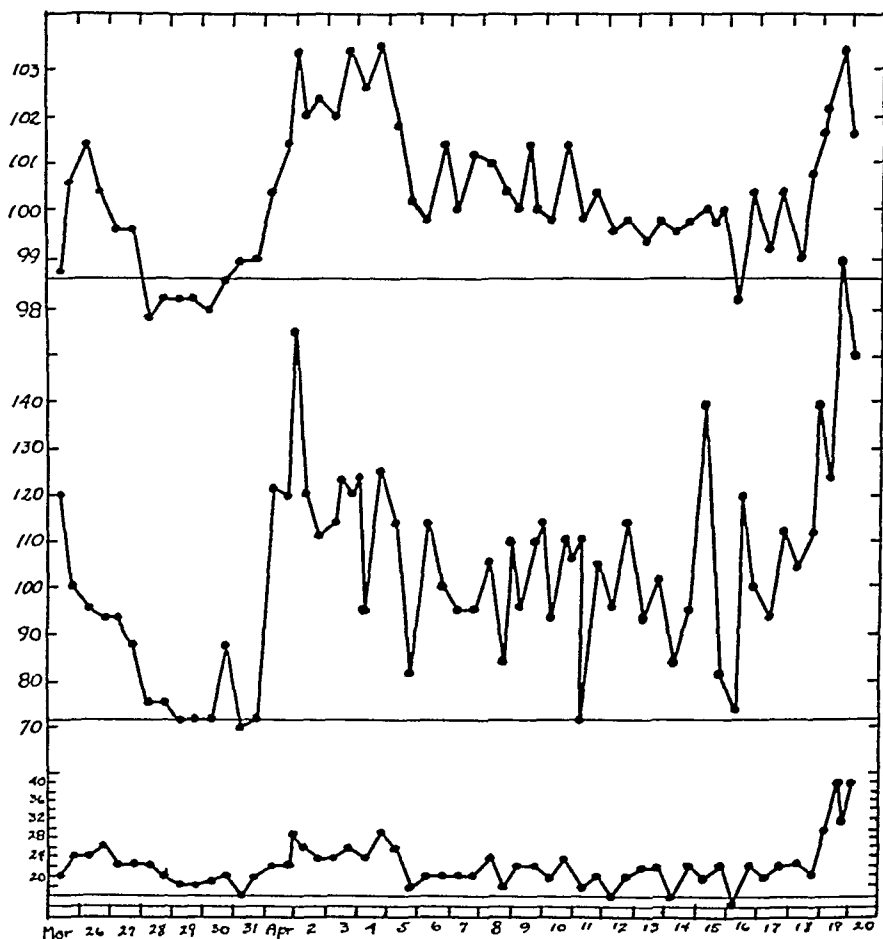


FIG 15 CURVES OF TEMPERATURE, PULSE AND RESPIRATIONS IN CASE 9

Note primary and secondary rise in temperature before abrupt tertiary (preterminal) rise. Marked variations in pulse rate were characteristic in this case.

markedly irregular, the rate increasing from 80 to 120 within a few seconds. Respirations were regular. The patient ground his teeth and was involuntary. The conjugate deviation of the eyes to the right and the bilateral Babinski persisted. The patient died on May 20, 1933.

An autopsy was performed by Dr. E. P. Palmer and Dr. Baldwin after

the body had been embalmed. A left sided bronchopneumonia associated with a left chronic adhesive pericarditis and pleuritis were found. There was also a dilatation of the stomach and upper intestinal tract. Evidence of infection was present in both renal pelvis.

The well fixed brain was brought to the laboratory through the courtesy of Dr. Carl W. Rand, who had been consulted by telephone as to the possible nature of the cerebral lesion. He suspected anoxemia as the cause of the

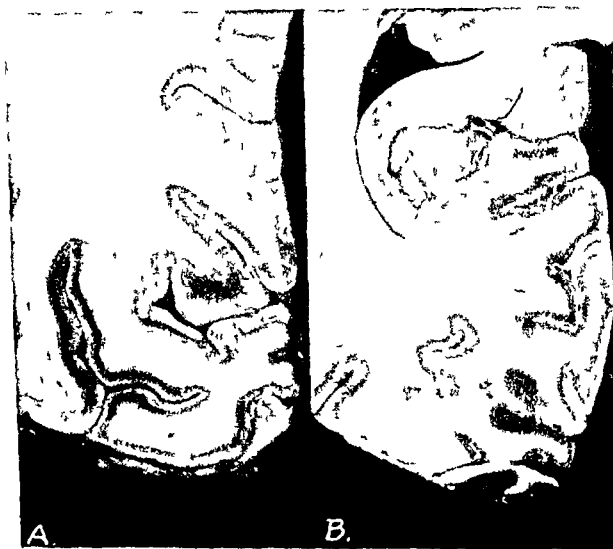


FIG. 16. CASE 9. SURVIVAL PERIOD 26 DAYS. SHOWING MARKED NECROSIS AND NARROWING OF CORTEX AT TWO LEVELS OF THE LEFT OCCIPITAL LOBE.

nervous manifestations and, knowing of my interest in the problem, graciously assisted in the procurement of the specimen.

A definite thickening and opacity, abnormal for an individual of this age, was found to be present. On cut section the cerebral cortex appeared remarkably thinned, granular and friable. This was particularly true in the occipital lobes, where the attenuated cortex had a yellowish color (fig. 16). The lenticular nucleus was likewise granular and necrotic. There were no

gross changes in the white substance of the brain and the brain stem and cerebellum seemed grossly normal

Blocks of tissue were taken from the frontal, parietal and occipital cortex and the hippocampus, from the lenticular nucleus, the caudal pons (level of vagus nucleus) and the cerebellum. Sections were stained or impregnated, according to the following techniques, Hematoxylin and eosin, scharlach R, Penfield's combined method, cyanin method for tigroid material, Courville-Krajan method for myelin sheaths and Cajal's and Bielschowsky's methods for neurofibrils

*Histopathology* There was a definite irregular thickening of the pia mater and arachnoid due to swelling of these membranes, and proliferation of their cells. In the pia this process was particularly marked in the region of the blood vessels. Small masses of calcareous material were present in the walls of some of the smaller vessels. Lymphocytes were found scattered throughout the leptomeninges or collected about the superficial vessels

Changes in the cerebral cortex were extremely variable (fig 17). In blocks from the frontal lobes, the degenerated process was limited to the intermediate and deeper layers, the decadent tissue having been replaced by a network of new formed blood vessels in the interstices of which were found transitional forms of microglia and compound granular corpuscles

Most of the nerve cells in the affected areas had disappeared, but those that remained presented a most unusual appearance. The persisting cells were stained a uniform deep purple and morphologically were typical of the so-called "calcified" nerve cells. The processes of these cells were evidently brittle, fragments being broken off sharply like a dried stick. These cells were for the most part engulfed by large phagocytic cells whose pink cytoplasm often contained two or more nuclei. With the Prussian blue method these "calcified" cells were found to contain iron (see frontispiece)

The parietal cortex was marked by patches of vascular proliferation in the deeper layers. In these less seriously affected regions many of the nerve cells showed advanced sclerotic change. In the cortex in the vicinity of the calcarine fissure where necrosis was grossly visible, there was an extensive disintegration of the intermediate cortex. The leptomeninges were adherent to a superficial layer of cortex, which in turn was detached more or less completely from a narrow residual band of deep cortex. An irregular, ragged, vascular scar bordered the defect on either side. The hippocampus showed no evident architectural alterations

The central portions of the lenticular nucleus were more or less completely replaced by a vascular scar presenting the same characteristics as the cortical one. Remains of "calcified" nerve cells were also present

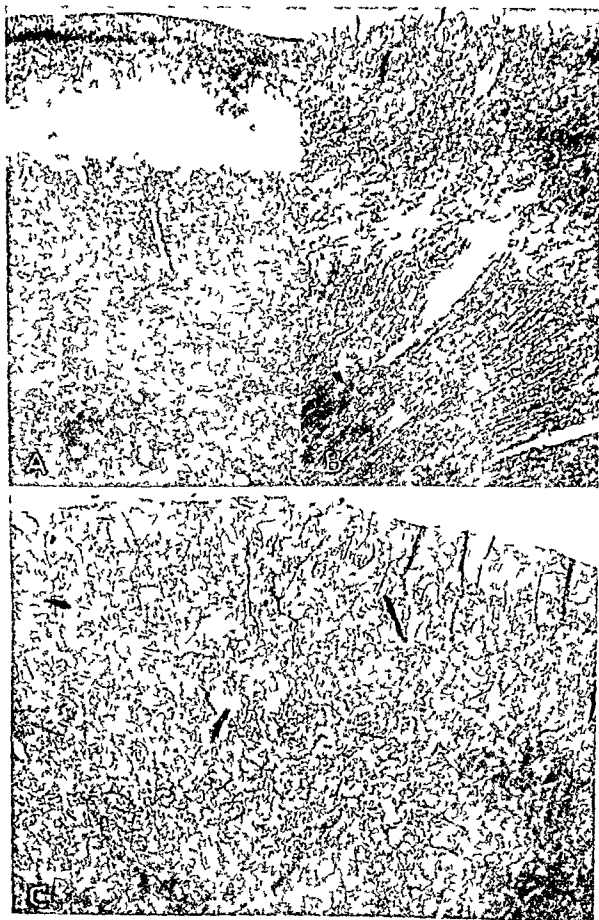


FIG 17 Case 9 1, showing marked subtotal necrosis of left occipital cortex. Reduced silver preparation  $\times 22$  B showing zonal necrosis in left midfrontal region. Reduced silver preparation  $\times 22$  C, circumscribed solid vascular scar in cortex of left superior parietal lobule. Penfield's combined method  $\times 35$

The nerve fibers constituting the white substance seemed unaltered. In the cortex, particularly in and adjacent to the necrotic areas, granulation and fragmentation of the axis cylinders were commonly found. End bulbs were also present in large numbers.

The cells of Purkinje showed loss of tigroid material and a universal but variable degree of degeneration of their neurofibrils. No architectural changes in the cerebellar cortex were noted. The cells of the nuclei in the medulla showed little appreciable alteration.

The vascular reaction in this case was the most striking and characteristic change. It was evidently the result of necrosis, occurring either in patches or zones. When necrosis had proceeded slowly and was limited in extent, this vascular scar was firm and circumscribed. In zones of rapid necrosis, as in the occipital lobe, the vascular scar was incomplete and formed only a ragged margin to the defect left by the decadent central strip of cortex. About some of the penetrating blood vessels in the superficial cortex, collections of lymphocytes were observed. In the walls of the blood vessels and in their perivascular spaces, globules of fat and yellow lipoidal pigment were found.

The neuroglial reaction to the degenerative process depended upon the local situation. The astrocytes were increased in number in the subpial glial layer, particularly where extensive necrosis of the cortex had taken place. Elsewhere the astrocytes were increased in the superficial cortical layers, transformation from the protoplasmic to the fibrous type having taken place. Fibrous astrocytes were also found to be strongly proliferated below the firm patchy vascular scars extending as an incomplete and irregular zone of gliosis into the underlying white substance.

The microglial reaction was unusually prominent in the necrotic areas, all transitional forms leading to the formation of fully developed phagocytes being present. In the white matter underlying the cortex the oligodendroglia were increased in number, particularly about the blood vessels, and these cells showed advanced stages of acute swelling.

*Comment.* A study of the cerebral tissues in this case was an unusual privilege, since it presented the changes occurring after an interval of 26 days. A later stage of variable degrees of necrosis was likewise illustrated. The phagocytosis of entire "calcified" nerve cells was an unusual and interesting phenomenon.

From a clinical standpoint, the possible relationship of alcoholism to asphyxia after nitrous oxide anesthesia is of interest. Alcohol is supposed to produce its effects by an interference with oxidation.

processes in the brain and a predisposition to cerebral anoxia may possibly be attributed to alcoholism

*Case 10 Nitrous oxide anesthesia for resection of fallopian tube (ectopic pregnancy) Incomplete recovery with residual parkinsonian syndrome Survival with mental defect Committed to a mental hospital*

A 30 year old married white woman was admitted to the Obstetrical Service of Dr Lyle G McNeile at the Los Angeles County General Hospital in a state of shock on August 21, 1931 A ruptured fallopian tube containing an ectopic pregnancy was resected  $4\frac{1}{2}$  hours later under nitrous oxide-oxygen ether anesthesia As the abdomen was being opened, the respirations suddenly ceased and were resumed only after a period of 10 to 12 minutes of energetically applied artificial respiration Although the respiratory movements finally became strong and regular, the pulse remained feeble and irregular

The patient subsequently developed a definite parkinsonian syndrome and marked mental impairment, ultimately requiring hospitalization in a mental hospital A more complete history of the mental changes will be reported in another contribution dealing with the psychosis following nitrous oxide anesthesia

*Comment* This case, the first in our series to survive the cerebral insult following nitrous oxide anesthesia, presents a number of interesting aspects A period of temporary improvement after the first period of coma, as seen in other cases of the series, led the writer to believe that recovery might occur Clinically, the lesion seemed to be one of advanced degeneration of the basal ganglia

The following case is also of interest, in that we have from a subjective viewpoint, the story of a patient who passed through an episode of cerebral anoxia and lived to tell the story

*Case 11 Residual lenticular syndrome in a patient surviving an anoxic episode after nitrous oxide anesthesia eight years before*

This was the case of a negro female of 27 years, who was admitted to the Los Angeles County General Hospital on September 5, 1932 with the complaint of pain in the lower abdomen and vaginal bleeding The condition cleared up spontaneously after a few days The writer was called in consultation because of the patient's idiotic facial expression

When the history had been gone into, it was learned that eight years before, February 1924, in this institution she had been operated upon for an

acute appendicitis She told her physician at the time that her heart was "weak" and a nitrous oxide-oxygen anesthesia was decided upon She did not regain consciousness thereafter for a period of unknown length, probably a number of days She learned afterwards that she had been deeply comatose for three days and later had generalized convulsions After recovering consciousness she was totally blind and it was three months before she was able to see She was also completely aphasic (motor) and was not able to make herself understood until six months later Since leaving the hospital the patient developed purposeless movements and tremors and experienced drawing sensations in the left thigh and back The limbs became rigid and contracted, and the patient was unable to walk

On examination the patient was found to have the facial expression of a feeble minded person and a slow hesitant speech. She was easily amused and episodes of involuntary laughter frequently occurred The pupils were equal, regular, and reacted to light and accommodation The optic disks were small and somewhat pale with narrow streaks of exudate along the vessels, especially on the left No nystagmus or palsies of the extraocular muscles were observed The deep reflexes were universally increased with no detectable tendency to lateralization The great toes were in a constant position of dorsiflexion Athetoid movements of the entire body were associated with a spastic rigidity of the extremities There was an atrophy of the small muscles of the hands Aside from a persistent strongly positive Kahn test of the blood, laboratory tests were essentially negative

The patient was observed for some days and discharged to her home on October 9, 1932

*Comment* It was of interest to get a story in this case of the patient's own experience with the disabling effects of cerebral anoxia, difficult though it was to secure it. It was unusual that complete blindness, presumably cortical, could clear up practically completely after a period of three months The residual symptoms were characteristically those of injury to the extra-pyramidal system

*Case 12 Nitrous oxide-oxygen-ether anesthesia for repair of perineal laceration after precipitate delivery Cyanosis and respiratory failure Generalized convulsions followed by state of restless delirium Recovery after transient aphasia, apraxia and visual disturbances*

A colored woman, 30 years old, was admitted in labor to the Obstetrical Service of Dr Edmund Lazard at the Los Angeles County Hospital on April 4, 1934 She gave a history of nausea up to the seventh month and of dizziness, headaches and visual disturbances during this, her third preg-

nancy A precipitate delivery, resulting in a second degree laceration, occurred seven hours after admission One hour later a nitrous oxide-oxygen (90 10) anesthetic was begun, but because patient fought the anesthetic, ether was also used (85 15 1/4) About 15 minutes later the patient suddenly stopped breathing At the moment the internal mucous membranes did not appear to be cyanosed If there was any change in the action of the heart at the time, it was not recorded Carbogen was administered immediately, and after an interval of about a minute the patient inhaled deeply These prolonged deep respirations continued for several minutes, gradually returning to the normal rate and regular rhythm The amplitude continued to be deep A few minutes later generalized convulsions made their appearance The blood pressure at this time was 100/68

The patient remained in a comatose state after the convulsions and a generalized increase in muscle tone associated with bilateral pathologic reflexes was observed The following day the patient was found to be completely aphasic and in a state of restless delirium The deep reflexes were universally increased, but more so on the left, associated with a left Babinski and right Gordon

Lumbar puncture revealed a clear, colorless fluid under very low pressure The non protein nitrogen of the blood was 18 mgm per 100 cc Albumin, not present before delivery, was now found in the urine A blood count was entirely normal

The patient's condition improved rapidly so that four days later she was apparently normal mentally The following day she complained of weakness in the right arm, blurring of vision and decreased auditory acuity Neurological examination two days later by Dr J M Nielsen and the writer disclosed a marked apraxia of the right hand After an interval of two days she was re examined, and a marked limitation of the visual fields was found, especially affecting the lower quadrants There was still some apraxia in the right hand The deep reflexes were increased on the right in the upper and on the left in the lower extremities There were no pathologic reflexes The temperature rose on one occasion to 100.8° and the pulse to 104 (fig 18)

She made a prompt recovery from all her symptoms and at the time of her discharge on April 20th, 17 days after onset of symptoms, no abnormalities could be found aside from a generalized increase in the deep reflexes When last seen in the post-natal clinic five weeks later she seemed to be entirely well

*Comment* This anesthetic accident occurred one day after the one described under Case 2 The anesthetic was given by the same



physician and with the same machine. When the nitrous oxide gas from the tank was analyzed and found to be normal, attention was directed to the machine as the possible source of the trouble. The findings have already been discussed under Case 2.

This case is of interest as an example of cerebral anoxia with complete recovery. The occurrence of a transient decrease in visual and

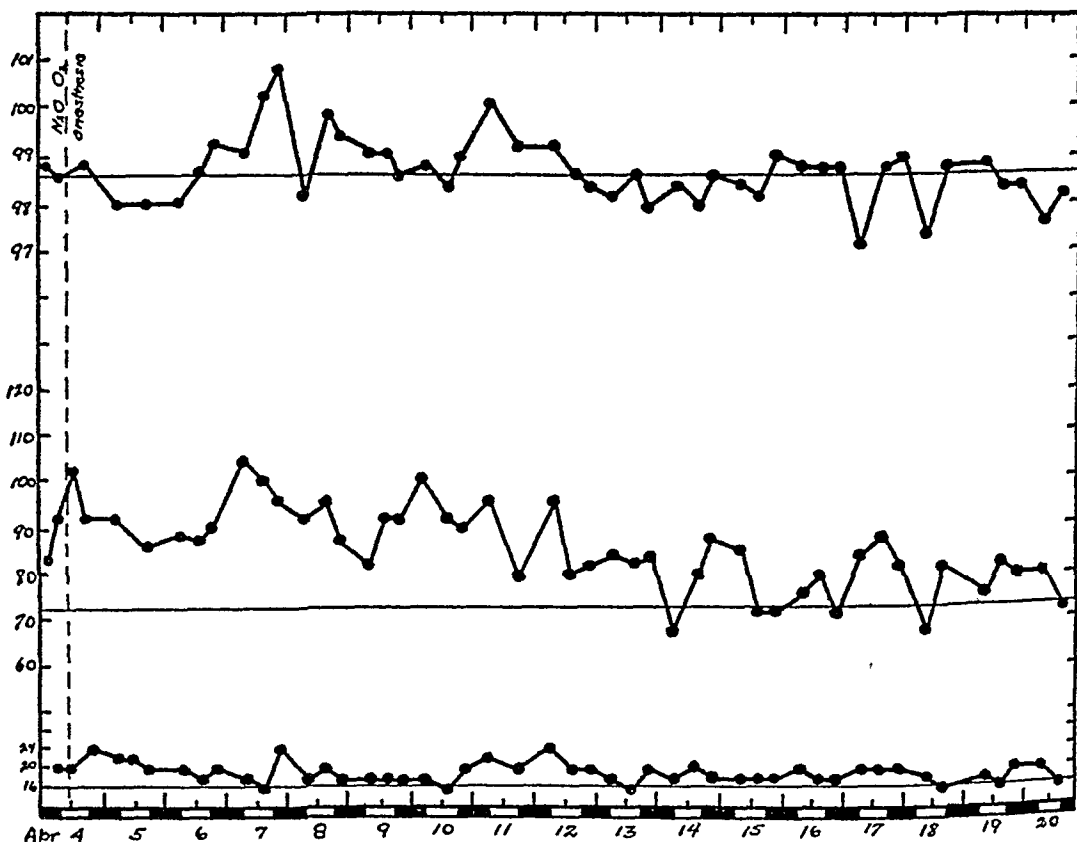


FIG 18 CURVES OF TEMPERATURE, PULSE AND RESPIRATIONS IN CASE 12. MINIMAL PRIMARY RISE FOLLOWED BY DELAYED SECONDARY RISE ASSOCIATED WITH A RECURRENCE OF NEUROLOGIC MANIFESTATIONS. COMPLETE RECOVERY.

auditory acuity illustrates the strange variability of the latent phenomena observed in some of these cases. Subsequent examination may disclose late residuals which were not picked up at the time of her discharge.

The following patient also recovered completely after suggestive symptoms had occurred after nitrous oxide anesthesia. The cortex

had evidently been affected only to a minor degree, since no actual period of respiratory failure had occurred. It is possible that the episode was due to other factors, the temporary and relative anoxemia playing but a minor rôle.

*Case 13 Cyanosis and muscular rigidity during short nitrous oxide anesthesia for curettement. Twenty-four hour period of restlessness. Respiratory irregularity and vomiting. Complete recovery.*

The patient, a female 28 years old, was admitted to the Obstetrical Service of Dr. Edmund Lazard at the Los Angeles County General Hospital on June 11, 1931, with the complaint of abdominal cramps and vaginal bleeding of four weeks duration. On the diagnosis of an incomplete abortion, a dilatation and curettage was performed on June 13, 1931, under nitrous oxide-oxygen anesthesia. The patient was cyanosed and rigid at times during the anesthetic but no respiratory irregularities were observed. While being removed from the operating table she began to scream and continued to do so for about thirty minutes. She was quieted with paraldehyde administered by stomach tube.

She was examined by the writer within an hour. At the moment she was restless though comatose, and purposeless movements of the extremities were observed. She could not be aroused by any form of painful stimulus. The temperature was 104° and the blood pressure 90/70. The pupils were small and reactionless to light. A spontaneous vertical and horizontal nystagmus was present. A peculiar staring sightless gaze occurred at intervals, associated at times with a conjugate deviation of the eyes to the right. When the head was placed in a neutral position, there was some tendency for it to deviate to the left. The deep reflexes were sluggish but equal throughout. A bilateral Babinski, Chaddock, Oppenheim and Gordon were associated with a bilateral unsustained ankle clonus. The superficial abdominal reflexes were abolished.

The patient later became more quiet and shortly regained consciousness. She vomited on several occasions. After a short febrile period, due probably to uterine infection (fig. 19), she became entirely well. She was discharged on June 20, 1930. When last heard from, there was no evidence of cerebral affection.

*Comment.* Were it not for the indisputable neurologic manifestations, one might be inclined to attribute the episode described above to any one of a number of causes. The presence of cyanosis and rigidity pointed to some difficulty with the anesthetic. A note on

the patient's record by the chief anesthetist, Dr Hessig, stated that in all the cases in which nitrous oxide had been administered in that particular surgical clinic, cyanosis and lack of muscular relaxation had occurred. This suggested the possibility that it was the nitrous

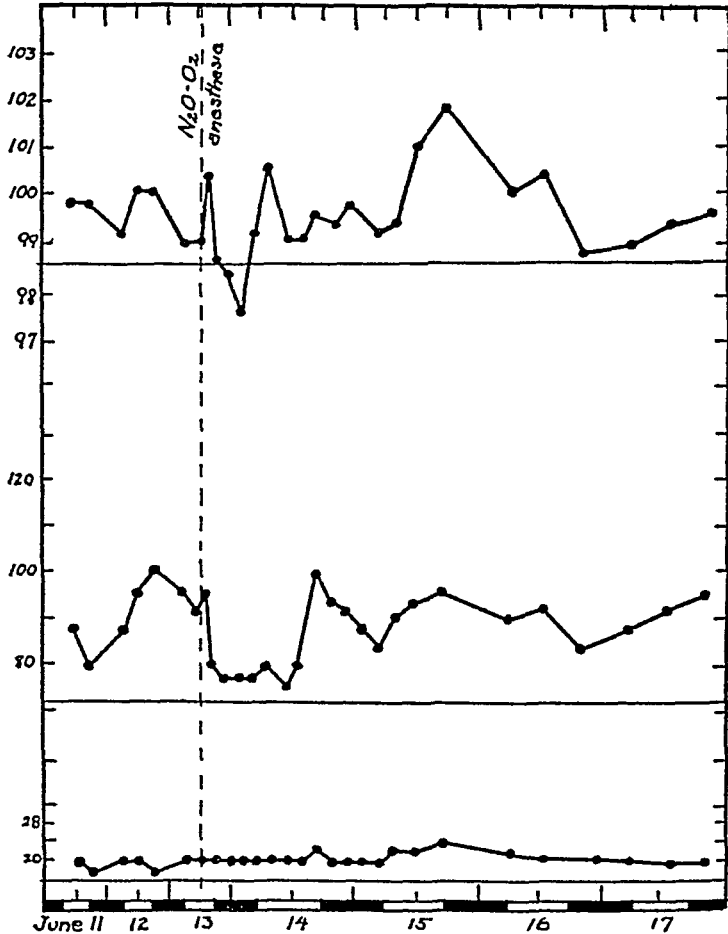


FIG 19 CURVES OF TEMPERATURE, PULSE AND RESPIRATIONS IN CASE 13 MINIMAL PRIMARY RISE IN TEMPERATURE PROBABLY ANOXEMIC IN ORIGIN SECONDARY RISE DUE TO PELVIC INFECTION COMPLETE RECOVERY FROM NEUROLOGIC SYMPTOMS IN 24 HOURS

oxide that was at fault Had some other factor intervened to cause temporary cessation of respirations, a full blown case of cerebral anoxia would likely have resulted <sup>3</sup>

<sup>3</sup> While this study has been in progress, a discussion with other physicians about the problem has brought to light a number of other instances of asphyxial manifestations

## CLINICAL CONSIDERATIONS

Since the majority of the cases in this series presented a more or less characteristic clinical picture, the manifestations may be divided into fairly well defined stages or periods. For purposes of convenience they may be designated as (a) prodromal stage, (b) a not invariable stage of respiratory or respiro-cardiac crisis, (c) stage of immediate reaction, and (d) a stage of apparent incomplete or complete recovery. In the fatal cases, (e), a terminal stage will be described.

The *stage of prodromal manifestations* is frequently but not constantly present. Since minor asphyxial manifestations occur occasionally in patients under nitrous oxide-oxygen anesthesia, the presence of such symptoms in patients who ultimately present serious symptoms is of uncertain significance. Since they are not invariably present, asphyxial symptoms preceding the actual onset of major cerebral phenomena, in some instances at least, may be coincidental. The prodromal manifestations observed in the 12 cases in which the story of the anesthetic period was available, were cyanosis and respiratory irregularity. Muscular twitchings, described by some as early anoxic symptoms, were not observed.

Cyanosis was observed during the anesthetic in 4 of the 12 cases (Cases 1, 2, 3 and 13). In Case 13 cyanosis was associated with muscular rigidity, both symptoms clearing up promptly when an airway was put in place. In 3 cases respiratory irregularities were noted, complete cessation for 2 minutes in Case 6, prolonged slow expiratory phase in Case 7 and deep irregular respirations in Case 8. In two cases (Cases 2 and 12), as though apprehensive of an impending tragedy, the patients fought the anesthetic, and ether was added to assist in hastening anesthesia. In 4 cases (Cases 4, 5 and 10) the first symptom was the sudden respiro-cardiac failure. In Case 9 the patient failed to regain consciousness after removal of the mask, convulsive seizures later becoming manifest.

The *stage of respiratory and cardiac crisis* is likewise not invariably present and presents some definite variations in the series of cases

with nitrous oxide. These cases have not been incorporated in this study since the writer had no direct clinical contact with them. The occurrence of mental aberrations suggestive of a psychoneurosis or actual psychosis was rather commonly noted. This phase of problem will be made the subject of a further study.

studied. In 8 out of 12 cases in which the anesthetic history is known, respiratory failure signaled the onset of the anoxic state. In some instances spontaneous respiration did not recur for as long as 20 minutes (Case 5). The exact length of this period is not always clearly determined, since artificial respiration was being administered in all cases. In 4 of these cases there was temporary cardiac failure as well, and in 2 others the heart beat was very rapid and weak and could scarcely be detected with the stethoscope. In instances of cardiac failure, there is an expected drop in blood pressure. During this interval it may drop to zero.

There is no constant relationship between respiratory and cardiac failure. As already stated, the heart beat may be strong and regular during the period of apnoea. It may be rapid and weak or absent altogether. The heart recovered first, where any difference had been noted (Case 5). Cardiac failure has been present invariably in the cases in this series when respiratory failure has been longer than momentary in duration. This, however, may not always be true. A prolonged circulatory failure must accentuate any existing cerebral damage, a matter to be considered in a later section.

In 4 cases there was no recognized cessation of respiration or cardiac action. In such instances the patient failed to regain consciousness after withdrawal of the anesthetic. Convulsions usually supervened within an hour. In the case of Yaskin (37) and that of Savage (38) no failure of respiration or circulation was recorded.

The *stage of immediate reaction* is characterized by the appearance of spontaneous respiration. The respiratory movements are at times shallow, gasping or jerking in character. In other instances they may be labored or stertorous in character. In still other instances the movements are slowed and deep. In the majority of cases studied the respiratory rate was definitely slowed, although immediately after the crisis it was increased at times (Case 5). Respirations are frequently irregular and jerky, especially when the excursions are shallow.

Irregular respiratory action may continue for a number of hours (Case 5) or even throughout the period of survival (Case 4), at times of a typical Cheyne-Stokes type. The so-called "periodic" alternation described in other types of anoxemia was not observed in any

of the cases coming under personal observation There was an increase in rate and decrease in amplitude of the respiratory movements during extensor spasms which were so frequently observed

The pupils, which are often dilated during the crisis, now assume their normal size At times they may be slightly unequal The temperature is usually elevated during this interval and perspiration, especially about the face and neck may be excessive This immediate rise of temperature after the crisis suggests a central disturbance of heat regulation

In those cases which are to terminate fatally or to have serious residual manifestations, a state of deep coma is usually present, from which the patient cannot be aroused In patients who recover within a short time, coma may be present in varying degrees, although at times the patient presents hysterical or maniacal manifestations (Case 13) In Savage's case (38) an alcoholic woman who presented a delirious state after anesthesia ultimately became demented

The *period of apparent or actual recovery* occurs after 24 hours in almost all patients surviving more than 48 hours In those with shorter survival periods it may not be obvious, particularly when complicating factors are present (Cases 1 and 2) In Caine's first case (35) definite improvement was noted after 7 hours, although the patient died  $17\frac{1}{2}$  hours after anesthesia While no definite rule can be laid down, the earlier and more definite the signs of recovery, the better the ultimate prognosis <sup>4</sup>

Unfortunately, improvement in the patient's condition is often short-lived and misleading, and a good prognosis made because of it is usually a mistaken one The promptness and extent of the early improvement gives some estimate of the ultimate prognosis, although at times almost complete recovery may occur in patients who eventually die (Case 2, Case 9, Caine (35) ) The evidences of improvement in patients with short survival periods are the occurrence of voluntary movement, restlessness, an increased response to external stimuli, resumption of a quiet, regular respiratory rate and a drop in

<sup>4</sup> The group of cases recovering completely after a few hours of coma or lethargy have been described in the section on "Toxicology" As a rule the patients in this group fail to regain consciousness after the anesthetic Convulsions usually ensue within a short while, although complete recovery often occurs within a few hours.

temperature The persistence of coma and of motor manifestations during the second and third days are ominous <sup>5</sup>

The *terminal stage* in those cases with a short survival period presents certain characteristic manifestations There is an invariable hyperthermia, usually a result of a gradually rising temperature At times, however, there is a rather abrupt pre-terminal rise in temperature, as was noted in the cases of Caine (Case 1 (35)) and Glynn (36). Perspiration is often profuse A concomitant rise in pulse and respiration rate is also present The centers of control for cardiac and respiratory action at times begin to fail appreciably before death, as indicated by a fall in pulse and respiration rates (Cases 1 and 5) In Case 4 death seemed to be the result of acute asphyxia, since gasping for breath was present until demise In other instances Cheyne-Stokes respiration occurs (Case 5) A generalized flaccidity with loss of all reflexes usually succeeds the hypertonic muscular state An interesting exception is found in Case 3, in which convulsions were noted within 3 hours of death They had been unusually persistent throughout the short survival period

Death may be due to other factors than the cerebral lesion Fulminating bronchopneumonia and the effects of asphyxia on the heart, liver and kidneys, perhaps play an important part in bringing about the fatal issue. In Case 8 a coincidental septicemia resulted in the patient's death after an apparent recovery from the anoxemic state

In the patients who survive a severe cerebral insult, the residual symptoms usually fall into one or more of three groups In the case of Savage (38) and Case 10 of this series, mental deterioration was the outstanding manifestation Some mental loss was also observed in Caine's second case (35) In Caine's third case (35) and in Cases 9 and 11 of this series athetoid movements were present In Case 10, in addition to the mental defect, a parkinsonian state was also present A marked visual defect was noted in Caine's third case (35), and in Case 9 These manifestations suggest that various portions of the brain may sustain the brunt of the anoxemic insult, an impression which pathologic findings seem to bear out

<sup>5</sup> The persistence of coma during this interval is not an absolute sign of impending death For example, Willett (39) recorded recovery in a patient who remained "practically asleep" for 4 days after nitrous oxide-oxygen anesthesia

In addition to a cursory survey of the various stages of the anoxic process, a study of the individual cerebral manifestations is also in order. A note on the laboratory findings in these cases will also be appended.

*Mental and emotional manifestations* The mental phenomena may be classified as early and late. The early manifestations are those found in the acute stage, the late ones occurring as residuals in those that survive the original cortical injury. Of the early manifestations coma is the most characteristic and is almost invariably present. Exceptions occur in rare instances in which a maniacal or delirious state occurs. Even then coma may follow for a variable interval. Immediately after the respiration cardiac crisis coma is profound and nothing can arouse the patient from it. This deep coma may persist with minor variations until death ensues (Case 6). It may be succeeded by other mental states (Cases 8, 9 and 11) or it may be followed by transient or permanent recovery (other cases in series). The more quickly and completely the return to consciousness the better the prognosis. If deep coma persists for four days, the prognosis is very grave. In fatal cases the coma again deepens before exitus. The depth of coma is an excellent indication as to the extent of depression of cortical function.

In less serious cases, a state of delirium or mania may occur just after the withdrawal of anesthesia. Reference to such occurrences has already been made. Hewitt (31) states that hysterical outbursts and transient hallucinatory states may follow administration of nitrous oxide. In Yaskin's case (37) emotional outbursts were described after a period of coma, and in Savage's case (38) anesthesia was followed by delirium. In Case 9 a period of coma was followed by delirium, due very likely to a developing septicemia. In Case 5 the patient, a young negro boy, cried out at intervals when coma became less deep. In Cases 7 and 13 involuntary laughing and crying were noted when the patients became more conscious.

Residual mental changes are evidently the result of extensive cortical degeneration. In Case 9, after regaining consciousness, the patient acted as though drunk. He presented a vacant staring look and his speech was thick. At times there were spells of screaming and grinding of his teeth. He became more irrational and again



temperature The persistence of coma and of motor manifestations during the second and third days are ominous <sup>5</sup>

The *terminal stage* in those cases with a short survival period presents certain characteristic manifestations There is an invariable hyperthermia, usually a result of a gradually rising temperature At times, however, there is a rather abrupt pre-terminal rise in temperature, as was noted in the cases of Caine (Case 1 (35)) and Glynn (36). Perspiration is often profuse A concomitant rise in pulse and respiration rate is also present The centers of control for cardiac and respiratory action at times begin to fail appreciably before death, as indicated by a fall in pulse and respiration rates (Cases 1 and 5). In Case 4 death seemed to be the result of acute asphyxia, since gasping for breath was present until demise In other instances Cheyne-Stokes respiration occurs (Case 5). A generalized flaccidity with loss of all reflexes usually succeeds the hypertonic muscular state An interesting exception is found in Case 3, in which convulsions were noted within 3 hours of death They had been unusually persistent throughout the short survival period

Death may be due to other factors than the cerebral lesion Fulminating bronchopneumonia and the effects of asphyxia on the heart, liver and kidneys, perhaps play an important part in bringing about the fatal issue In Case 8 a coincidental septicemia resulted in the patient's death after an apparent recovery from the anoxic state.

In the patients who survive a severe cerebral insult, the residual symptoms usually fall into one or more of three groups In the case of Savage (38) and Case 10 of this series, mental deterioration was the outstanding manifestation Some mental loss was also observed in Caine's second case (35) In Caine's third case (35) and in Cases 9 and 11 of this series athetoid movements were present In Case 10, in addition to the mental defect, a parkinsonian state was also present A marked visual defect was noted in Caine's third case (35), and in Case 9 These manifestations suggest that various portions of the brain may sustain the brunt of the anoxic insult, an impression which pathologic findings seem to bear out

<sup>5</sup> The persistence of coma during this interval is not an absolute sign of impending death For example, Willett (39) recorded recovery in a patient who remained "practically asleep" for 4 days after nitrous oxide-oxygen anesthesia

In addition to a cursory survey of the various stages of the anoxic process, a study of the individual cerebral manifestations is also in order. A note on the laboratory findings in these cases will also be appended.

*Mental and emotional manifestations* The mental phenomena may be classified as early and late. The early manifestations are those found in the acute stage, the late ones occurring as residuals in those that survive the original cortical injury. Of the early manifestations coma is the most characteristic and is almost invariably present. Exceptions occur in rare instances in which a maniacal or delirious state occurs. Even then coma may follow for a variable interval. Immediately after the respiration-cardiac crisis coma is profound and nothing can arouse the patient from it. This deep coma may persist with minor variations until death ensues (Case 6). It may be succeeded by other mental states (Cases 8, 9 and 11) or it may be followed by transient or permanent recovery (other cases in series). The more quickly and completely the return to consciousness the better the prognosis. If deep coma persists for four days, the prognosis is very grave. In fatal cases the coma again deepens before exitus. The depth of coma is an excellent indication as to the extent of depression of cortical function.

In less serious cases, a state of delirium or mania may occur just after the withdrawal of anesthesia. Reference to such occurrences has already been made. Hewitt (31) states that hysterical outbursts and transient hallucinatory states may follow administration of nitrous oxide. In Yaskin's case (37) emotional outbursts were described after a period of coma, and in Savage's case (38) anesthesia was followed by delirium. In Case 9 a period of coma was followed by delirium, due very likely to a developing septicemia. In Case 5 the patient, a young negro boy, cried out at intervals when coma became less deep. In Cases 7 and 13 involuntary laughing and crying were noted when the patients became more conscious.

Residual mental changes are evidently the result of extensive cortical degeneration. In Case 9, after regaining consciousness, the patient acted as though drunk. He presented a vacant staring look and his speech was thick. At times there were spells of screaming and grinding of his teeth. He became more irrational and again

sank into coma before his death, 26 days after anesthesia. In Case 10 the patient became demented and was committed to a mental hospital asylum. In Case 11, after 8 years, the patient presented involuntary laughter and a childish mentality. Ultimate insanity has been described by Hewitt (31) and Savage (38).

*Motor manifestations* The motor manifestations following anoxemia of nitrous oxide origin, point to involvement of the pyramidal, extra-pyramidal and coordinating systems. The *pyramidal tract signs* vary, depending upon the time of examination. Immediately after the crisis under nitrous oxide, bilaterally increased deep reflexes, pathologic reflexes and ankle clonus are present. The superficial reflexes are absent and do not return in patients soon to die. They may reappear as the stupor lessens. Irritative motor manifestations soon appear, usually within 1 to 2 hours. Convulsive seizures, usually generalized, though at times appearing first on one side, are most common.<sup>6</sup> They may persist in spite of sedation until the time of death (Case 3), in which case they may be a contributing factor to the fatal issue (exhaustion). Generalized rigidity occurring particularly as extensor spasms is also common. These spasms may be associated with generalized convulsions or may occur without them. The condition was present in 7 of our cases. These extensor spasms gave rise to a picture of decerebrate rigidity, suggesting a lesion of the midbrain.

The patient who has been in a state of coma and has presented little voluntary motor activity, suddenly becomes rigid in extension. This rigidity may be generalized, affect the extremities on one side or the other, at times alternating between the two, or affecting but one group of muscles. Local twitching movements may occur. The hands may assume a tetanic position and a Magnus-de Kleijn phenomenon may be elicited. The pupils

<sup>6</sup> Convulsive seizures are by no means indicative of a fatal outcome in cases of anoxemia due to nitrous oxide, although it proved to be so in most of the cases in the series. As has already been shown in a previous section, convulsive seizures, particularly in children, may be followed quite promptly by recovery. They have been believed to be of anoxemic origin by other observers (Clement (30), Hewitt (31), Rood and Webber (32)).

The lateralizing aspects of certain of these motor phenomena (unilateral convulsions and conjugate deviation of the head and eyes) may delude the clinical observer into a diagnosis of a focal lesion. It will be shown that the cortical injury is by no means generalized or even symmetrical, and that irregularities in lateralizing phenomena should occur is not surprising.

dilate, respirations become faster, shallower and often irregular, the pulse rate becomes more rapid. The blood pressure is somewhat elevated. The face may become flushed. After a few moments the muscular rigidity abates, the respiration and pulse rate become slower, the pupils contract and the patient resumes his former status.

Deviation of the head and eyes to one side or the other was noted in 5 cases. Fibrillary twitchings were also noted at times. In Case 8 fibrillary twitchings of the tongue and jaw were of unusual interest.

Generalized spasticity and contractures were noted in Case 11 as a late residual condition associated with athetoid movements, involuntary laughter and a childish mentality.

*Extrapyramidal signs* As proven by postmortem studies, the corpus striatum and in particular the lenticular nuclei are at times the seat of degenerative changes. Clinical evidence of striatal disease becomes particularly evident, however, in those patients who survive the early days of cerebral damage. In Case 9, for example, a man who survived the anesthetic for 26 days presented irregular and uncontrolled movements of the extremities. Athetoid movements were present also in Case 11, when studied 8 years after the anesthetic episode.

In Case 10 early manifestations of a parkinsonian state were presented and grew progressively more marked as time went on. Ultimately the mask-like, expressionless facies, the generalized rigidity and characteristic tremor could not be mistaken.

*Incoordination* as evidence of degeneration of cells of the cerebellar cortex was not a common observation. The reasons for this are evident. In the acute stage the patient is unable to cooperate. Those who survive either recover promptly or develop rigidities which interfere with the usual cerebellar tests. In Case 9 an alert observer noted definite signs of incoordination in the right arm during an interval when other motor manifestations did not conflict.

*Sensory phenomena* are unusual. In Case 9 where mental lucidity permitted study during the longer survival period, the patient complained of a peculiar feeling of swelling of the right hand.

*Visual symptoms* Perhaps none of the localizing cerebral manifestations are of more interest than the visual ones. They were elicited, of course, only in those patients in whom sufficient recovery

occurred to permit the patient to describe his symptoms. It was present in Caine's third case (35) at the end of ten years. In Case 11 the patient was blind for three months after nitrous oxide anesthesia. The optic discs were paler than normal. In Case 9 failure of vision proved to be due to extensive necrosis of the visual cortex.

*Effect of anoxemia on the "vital centers"* Attention has already been given to the effects of the anoxic state on temperature, pulse and respiration during the various stages. There was usually no change in the blood pressure during the period of survival. During the interval of cardiac failure the blood pressure often drops alarmingly and may not be measurable. In one case (Case 7) the blood pressure was found to be elevated during labor on admission. It remained elevated on most occasions during the survival period of 6 days. There is evidently no characteristic effect of anoxemia on the blood pressure in this group of cases.

*Vasomotor variations* have also been observed. Flushing of the face, increased perspiration, and, as has already been intimated, the intermittent occurrence of the cerebral manifestations themselves may be due to vasomotor fluctuation. These peculiar attacks probably represent some temporary alteration in blood supply, perhaps due to vasomotor spasm. The occurrence of such attacks indicate grave damage to the cerebral cortex, and all of the cases presenting this syndrome terminated fatally.

*Laboratory findings* The spinal fluid was usually normal. In three instances the pressure was increased, in Case 6 the pressure was 250 mm. the day of the patient's death, five days after onset of cerebral injury. This patient also showed a trace of globulin. In Case 3 a trace of globulin was also recorded. In a patient who became insane (Case 10), the pressure was also elevated (not measured) 8 days after the onset. The colloidal benzoin curve showed reduction in the middle tubes. In Case 7 the spinal pressure was well over 400 the day before death. There is evidently no characteristic response of the spinal fluid to the anoxic state, although the pressure is frequently found to be increased.

The white blood count was normal in most instances. In Case 1 a leukocytosis of 19,500 of undetermined etiology was recorded. There was no appreciable change in the red blood count or percentage

of hemoglobin. The urine may show a high specific gravity and albumin and acetone are frequently present. The percentage of albumin increases progressively in most instances. This is to be explained on the basis of lowered fluid intake, and to the effect of asphyxia on the kidney. The increased sugar content of the blood and the presence of glycosuria as observed in some instances were likely due to intravenous administration of glucose. Of three fatal cases surviving only a few days (Cases 3, 4 and 6) a slight elevation of the non protein nitrogen (44, 41 and 41 mgs per 100 cc of blood, respectively) was present.

*Pathogenesis of cerebral anoxia due to nitrous oxide* In an attempt to explain the serious cerebral symptoms resulting from nitrous oxide anesthesia, several questions demand attention. Are there predisposing factors which favor the development of cerebral damage? What part do the impurities of nitrous oxide and mechanical defects in its administration play in producing these symptoms? What is the essential cause of the advanced and dangerous stage of anoxemia? What is the mechanism of cerebral injury?

As a preliminary step to a consideration of these questions a brief survey of the action of nitrous oxide is in order. It seems to be established that while nitrous oxide has a definite narcotic action on nerve cells, this action is markedly accentuated by the accompanying anoxemia. Anoxemia under these circumstances is of the anoxic type, viz —with a lowered tension and amounts of oxygen present in the blood. Furthermore, the oxygen present is probably less readily available to the tissues because of the lowered  $\text{CO}_2$  tension which retards the breaking down of oxyhemoglobin and removes the normal stimulus of the respiratory center. It also seems evident that the depth of anesthesia is dependent, not so much on the concentration of nitrous oxide in the blood plasma, which seems to be fairly constant, as on the lessened amount of oxygen. In deep anesthesia, therefore, the anoxemic state approaches more or less closely the margin of safety. As has already been stated, the absence of cyanosis does not necessarily indicate the absence of anoxemia.

*Predisposing factors* Are there factors existing in the patient, either congenital or acquired, which favor the development of a critical anoxemic state? The possible aspects of the problem which

NUMBER	AGE	SEX	OPERATION	DURATION OF ANESTHESIA	PRODROMATA	CARDIAC RESPIRATORY FAILURE	CR
1*	46	M	Exploration for lung abscess	N <sub>2</sub> O-O <sub>2</sub> for 45 minutes	Cyanosis	0	Coma after 1 1/2 hours. Deviation
2	21	F	Episiotomy and repair	N <sub>2</sub> O-O <sub>2</sub> for 4 minutes N <sub>2</sub> O-O <sub>2</sub> + ether for 30 minutes	Cyanosis Fought anesthesia	Respiratory failure 1 minute	Residual 1 hour 1 left SI
3	42	M	Extraction of teeth	N <sub>2</sub> O-O <sub>2</sub> for 30 minutes	Cyanosis	0	Residual 1 1/2 hours after rigidity
4	29	F	Biopsy	N <sub>2</sub> O-O <sub>2</sub> for only few minutes	0	Cardiorespiratory failure 4-5 minutes	Residual 1 hour 1/2
5	6	M	Curettage osteomyelitis right tibia	N <sub>2</sub> O-O <sub>2</sub> for 1 hour	0	Respiratory failure 20 minutes Cardiorespiratory failure 3-4 minutes	Residual 1 hour 1 left Sp
6	43	F	Hysterectomy and cauterization cervix	Sodium amytal Spinal (novocaine) N <sub>2</sub> O-O <sub>2</sub> for 10 minutes	Respiratory failure 2 minutes	Cardiorespiratory failure 4-5 minutes	Residual 1/2 Extensor
7	17	F.	Episiotomy and repair	N <sub>2</sub> O-O <sub>2</sub> for few minutes N <sub>2</sub> O-O <sub>2</sub> + ether 25 minutes	Prolonged slow expiration	0	Residual 1/2 generaliz
8	35	F	Dilatation curettage	N <sub>2</sub> O-O <sub>2</sub> for 12 minutes	Deep irregular respiration	Respiratory failure 2 minutes Pulse weak and rapid	Residual 1/2 tongue and rigidity
9	27	M	Extraction teeth	Sodium amytal N <sub>2</sub> O-O <sub>2</sub> for 40 minutes	0	Cardiorespiratory failure ? minutes	Residual 1/2 and ext head and

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NUMBER	AGE	SEX	OPERATION	DURATION OF ANESTHESIA	PRODROMATA	CARDIO-RESPIRATORY FAILURE
10	30	F	Resection of fallopian tube	N <sub>2</sub> O-O <sub>2</sub> for 30 minutes	0	Respiratory failure 1 minute and rapid ?
11	27	F.	Appendectomy 8 years before	N <sub>2</sub> O-O <sub>2</sub> , duration unknown	?	
12	30	F.	Repair perineal laceration after delivery	N <sub>2</sub> O-O <sub>2</sub> + ether for 12 minutes	Fought anesthesia	Respiratory failure 1 minute (diac status known) 0
13	28	F	Dilatation and curettage	N <sub>2</sub> O-O <sub>2</sub> for only few minutes	Cyanosis Muscular rigidity	

\* History of previous anoxic episode after nitrous oxide anesthesia—see case report.

de anoxemia

ONS	STAGE OF REACTION	STAGE OF APPARENT RECOVERY	TERMINAL STAGE	SURVIVAL PERIOD
Convulsions deep reflexes	Not evident Convulsions controlled by sedatives	Not evident Condition grew progressively worse	Hyperthermia Generalized flaccidity Terminal fall in P and R	40 hours
ons after 1 and eyes to exes	Convulsions Slowed deep respirations for 4-5 hours	Minor voluntary movements Coma less deep	Hyperthermia Increased respiratory and pulse rates Generalized flaccidity	43 hours
ons 15 min Decerebrate	Stertorous labored respirations Cyanosis	Fall T P R 28 hours after anesthesia Controlled convulsions Coma less deep	Hyperthermia Increased respiration and pulse rates Pulmonary edema Convulsions	64 hours
ons within 1 ensor rigidity	Convulsions Vomiting Labored, shallow respirations	Not evident Increased voluntary activity after 24 hours	Hyperthermia Increased respiration and pulse rates Gasping for breath Cyanosis	3 days, 5 hours
sions after 1 and eyes to rigidity	Shallow, gasping respirations Hypertonicity upper extremities	Increased voluntary movements Reacted to painful stimuli Frequent outcnes Coma less deep	Hyperthermia Cheyne Stokes respiration Terminal drop in respiration and pulse rates	4 days, 7 hours
ar twitchings	Slow, labored gasping respiration Feeble pulse	Not evident	Hyperthermia Increased respiration and pulse rate Tonic state less marked	5 days, 5 hours
sided then s after 1½ hours	Slow shallow respirations after anesthesia	Coma less deep after 24 hours Restless Emotional outbursts	Hyperthermia Abrupt preterminal rise in respiration and pulse rates Deepening coma General flaccidity	6 days, 13 hours
ching of the asms extensor ins (sepsis?)	Shallow jerky gasping respiration Pulse slowed	Uncertain (septicemia)	Uncertain Death due to septicemia (septic abortion)	19 days
lar twitchings ns Deviation t	Jerky shallow respirations Pulse rapid during extensor spasms	After 24 hours Irrational and restless Motor weakness Aimless movements (apraxia) Aphasia Blindness	Recurrent coma Hyperthermia Increased respiration and pulse rates	26 days

1 cases

CEREBRAL MANIFESTATIONS	COURSE	OUTCOME
perform movements Defective mentality Diminished deep reflexes Convulsions Residual coma marked motor aphasia Tranitory complete blindness	Seemed clear mentally after 24 hours Later mental enfeeblement followed by slight recovery for 1 month Recovery from coma after few days Gradual improvement for 6 months Condition stationary since	Residual mental defect, Parkinsonian syndrome Committed to insane asylum Residual athetoid and choreiform movements Emotional instability Mental defect—all after 8 years
idual coma Deep slowed respirations, rate increased later	Improved for period of 5 days, then re appearance of visual and apraxia which remained for several days	Apparently complete recovery at end of 2 weeks
nsistent period of coma Emotional outbursts Deviation of head to left Pathological re-	Prompt improvement of all symptoms	Complete recovery in 36 hours



need consideration in this connection may be divided into three groups,—congenital predispositions (*idiosyncrasy*, *robust habitus*, *status thymicus*), acquired conditions (pulmonary diseases, blood dyscrasias, pre-existing cerebral diseases) and disturbed reflex arcs (carotid sinus reflexes, reflexes from the lower abdomen)

The problem of *idiosyncrasy* is perennially with us and always a difficult one to settle. Many of the untoward reactions to drugs are laid at its door, whatever this term may mean. In the case of nitrous oxide it may indicate an increased susceptibility of the respiratory center to its depressive effects. Susceptibility to drugs in general, like allergy, is characterized by the circumstance that in affected individuals a small dose is sufficient to produce serious symptoms. If this analogy is carried out, *idiosyncrasy* might be suspected when serious manifestations appeared shortly after the anesthetic was begun. Cases of sudden death under nitrous oxide have been explained by some observers, (i e., Adams (21)) in this manner. In but one case in this series can this factor be given serious consideration (Case 4). There was a sudden respiration-cardiac failure a few moments after the induction of nitrous oxide anesthesia.

*Status thymicus* has been blamed for sudden death under nitrous oxide anesthesia. In the cases of sudden death described by Davis (20) and Owen (19) a persistent thymus was found at autopsy and exitus was attributed to it. No evidence of a persistent thymus or of hypertrophied lymphatic tissue was found in any of the fatal cases in this series. It would seem unlikely that this condition would seriously influence the production of late symptoms referable to cerebral damage as described in this series of cases.

*Alcoholism*. It has been suspected by some that alcohol favors the development of convulsive seizures under nitrous oxide (32). In Case 9 there was a history of alcoholism, and it was thought that the patient had imbibed quite freely before going into the dentist's office. This possibility needs to be given more attention in these instances. In the majority of cases, however, no history of alcoholism could be elicited.

Males of *robust build* have been considered to have some peculiar predisposition to develop untoward symptoms under nitrous oxide anesthesia. According to Rood and Webber (32) convulsions are

particularly apt to occur in alcoholics and in heavily built individuals. They did not consider the possible reasons for such an eventuality, and the writer has nothing further to add in this regard from his experience with nitrous oxide anesthesia.

*Influence of disease* In order for disease of itself to influence the course of anesthesia, it must logically affect those systems directly concerned in anesthesia, viz—the lungs, heart, blood or brain. Reference has already been made to the influence of *pulmonary conditions* on anoxemia. Any condition which reduces the volume of the lung available for aeration of the blood obviously favors the development of anoxemia. It is noteworthy that in three of the fatal cases pulmonary lesions were present (Case 1, pulmonary abscess, Case 5, pulmonary tuberculosis, Case 7, pulmonary embolism). It is evident, however, that other causes must co-exist since nitrous oxide has been administered to many patients with pulmonary conditions without any untoward effects whatever.

The influence of *heart disease* in the production of anoxemic states has been given little attention insofar as nitrous oxide is concerned. Haveman (17) and Ramsey (18) have observed that acute dilatation of the heart is frequently found at autopsy after sudden death under nitrous oxide anesthesia during operations on the thyroid gland. Thyrotoxicosis may be a predisposing factor in these cases. It seems unlikely that cardiac disease is *per se* an important factor in the production of the anoxemic state. It is possible that a pre-existing myocardial weakness might be aggravated by anoxemia. Only in one case (Case 11), and in that an indefinite one, was there history of cardiac trouble. This patient recovered with residual manifestations.

When *anemia* of any serious degree is present, one type of anoxemia is produced. In this type, owing to a decreased amount of available hemoglobin, less oxygen is carried in the blood. Since the oxygen tension is normal, tissue oxidation is maintained as long as too great demands are not made upon this supply. However, if the anoxic type of anoxemia be superimposed on the anemic type, serious symptoms might easily occur. In Case 6, the anoxemic state may have been favored, in view of the excessive intra-abdominal hemorrhage incident to the ruptured tubal pregnancy.

As to *cerebral disease* being a predisposing factor to anoxic cortical

degeneration, nothing definite is known. It is quite generally accepted that nitrous oxide can safely be given in the presence of a focal cerebral lesion, even in operations for tumor of the brain. The only type of cerebral lesion likely to predispose to anoxic changes would be a diffuse lesion of the smaller blood vessels, as in some instances of arteriosclerosis or in syphilitic endarteritis.

As to *reflex effects* predisposing to anoxemic states, two possibilities need be considered. It has been found that reflexes from the carotid sinus definitely influence the respiratory center.<sup>7</sup> Respiratory and cardiac failure may result from a disturbance of this reflex. It was on this basis that Downs (22) assumed that sudden death under nitrous oxide might be the result of a perverted reflex due to its direct action on the sinus or on the nervous system. He warned against local pressure at the angle of the jaw. This theory might explain sudden death under this anesthetic in instances of focal lesions in the neck, such as an abscess, as reported by Dent (23). Whether the respiro-cardiac failure observed in the cases in this series was due to a disturbed sinus reflex is not clear, and the question demands further study.

It is of interest to note that a number of patients demonstrating serious anoxemic manifestations were being operated upon for some pelvic disease (7 of 13 cases). While this is probably only a coincidence, the possibility of some disturbed reflex should be considered.

*Factors of anesthesia in the production of anoxemia* The anoxemic state which is an integral part of nitrous oxide anesthesia may be accentuated to a dangerous degree by any one or more of a number of factors. In a consideration of anoxemia following the use of general anesthetics, Evans (41) states that obstruction of the upper respiratory passages, diseases of the heart or lungs, abdominal distention, hemorrhage or central nervous depression (as depressing effects of preanesthetic drugs or of the anesthetic itself) may be the cause of postanesthetic anoxemias. A number of these factors have been considered in other connections. Only those which are inti-

<sup>7</sup> It has been known for some time, for example, that section of the nerves about the carotid sinus in experimental animals, frequently resulted in sudden death. It is believed that impulses from the sinus are transmitted by the vagus to the respiratory center and assist in the maintenance of activity of the center. Removal of these impulses have been considered as the cause of death in such instances (40).

mately associated with nitrous oxide itself and its administration will be considered here

The possibilities of *impurities of nitrous oxide* as a cause of anoxic manifestations has been given little or no attention in recent years. With improved methods of manufacture and storage, the question of purity of the gas has been left quite largely in the hands of the manufacturer. In the past attention has been drawn to such impurities as chlorides and oxides or to more complex compounds, as hydrazins and hydroxylamins (42). More recently Chaney and Lombard (43) developed a new method for analysis of nitrous oxide. Utilizing this method, Chaney (44) found that in tanks of nitrous oxide which had produced serious cerebral manifestations, an excess of inert nitrogen was present. In the cases which have come under my personal attention, nitrous oxide from the tanks which produced anoxic symptoms was found in two instances to contain an excess of inert nitrogen. This should be thought of as one of the possible factors in cases of cerebral anoxia.

*Defects in the apparatus* may also be a source of trouble. When looking for a possible clue to the difficulty in two cases which immediately succeeded one another, the gas from the tank used was analyzed without finding any impurities. The apparatus was then examined by measuring the percentages of nitrous oxide and oxygen at various indicated levels. It was found that 100 per cent nitrous oxide might be delivered when the dial registered 90 per cent. As much as 90 per cent nitrous oxide was delivered at points indicating 50 to 90 per cent. Examination of the apparatus itself disclosed a shortening through wear of the plunger in the needle valve controlling the flow of nitrous oxide. Examination of another machine after a similar episode disclosed the fact that in the higher concentrations, less than the registered amount of gas was being delivered, while in the lower concentrations the reverse was true. The possibilities of mechanical defects must be considered when old and possibly worn machines have been used.

*Poorly trained anesthetists*, or perhaps more accurately stated, individuals without training or unfamiliar with the apparatus used, may be responsible for serious untoward results. Since nitrous oxide and machines for its administration have become so perfected as to make

them almost "fool-proof," the warning of older anesthetists as to the potential dangers of this anesthetic have been to some extent disregarded. Fortunately, anesthesia has become a science in itself and in a well regulated hospital the patient has little to fear, and it is likely that but few cases of cerebral anoxia can be attributed to inefficiency or carelessness on the part of the anesthetist. The tragedy may occur in the hands of a skilled and conscientious physician when the proper combination of factors exists. Each case must stand as a law unto itself, and even an approximate conclusion can be reached only when all possibilities have been given due consideration.

The effects of *obstruction of the upper respiratory passages*, as commonly experienced when the tongue drops back to occlude the pharynx, is so familiar as to preclude discussion. The interference with oxygen supply in this way might be a contributing factor in the production of anoxemia. It is probably of doubtful influence in the production of serious symptoms. In only one case (Case 13) was note made of this experience. This patient recovered completely.

*The cause of pathologic anoxemia in nitrous oxide anesthesia*. From the study of this series of cases and of those reported in literature, it seems evident that not all instances have a similar mode of development. The factors which must be thought of are so numerous that an exact analysis of any given case is extremely difficult. The cases divide themselves into two groups in so far as the onset of symptoms is concerned. In the first group there is a sudden onset of respiratory and heart failure, or respiratory failure alone, occurring at a variable interval after the beginning of anesthesia. In the second group, the patient fails to regain consciousness after anesthesia, few or no suggestive symptoms having occurred before that time.

The cases falling in the first group are the ones most commonly observed, and in this group the anoxemic state is the easiest to explain. The patient under nitrous oxide anesthesia is already under the influence of an anoxic anoxemia. The oxygen saturation becomes less and less as the deeper stages are reached. When there is a sudden respiratory and cardiac failure, two further serious factors become present. Until artificial respiration is resorted to, there is no additional supply of alveolar oxygen available, although the respiratory exchange in the lungs continues. Furthermore, because

the circulation has failed, an element of stagnation is superimposed. The narrow margin of available oxygen is promptly exhausted and the body tissues are exposed to the effects of serious oxygen want. Since the cerebral tissues have so active a rate of oxygen consumption normally and are so susceptible to a lack of it, it is easy to see why the cerebral damage is so extensive.

If the respiration alone fails, the oxygen saturation of the blood is reduced to a dangerous level. The blood serum overcharged with nitrous oxide continues to exert its malignant effect upon the nerve cells already depressed to the limit.

It is necessary in this connection to pause long enough in our story to enquire what the cause of the respiratory and cardiac failure might be. There is no direct evidence available which can be used to answer the question. There are two possibilities which may be thought of,—(1) the effect of an increasing anoxemia on the respiratory and cardiac centers, and (2) the influence of pulmonary embolism, which in some instances may play an important rôle in this connection.

It has long been known that the respiratory center is much more susceptible to the accumulation of  $\text{CO}_2$  than it is to a lack of oxygen, and that under such circumstances there is a marked increase in the depth of breathing, but only a moderate increase in frequency. On the other hand anoxemia produces a marked increase in frequency but only a moderate increase in depth of breathing. This increased respiratory rate removes much of the usual amount of  $\text{CO}_2$ , the source of stimulus to the center. As breathing becomes shallower and more frequent the state of anoxemia deepens and a failure of the respiratory center is threatened (45).

If this situation occurs under nitrous oxide, the respiratory center fails. When this happens, the state of anoxemia immediately becomes accentuated and lethal damage to the cerebral cortex may occur before normal respiration is established. One experience which strengthens this hypothesis is the prolonged interval during which artificial respiration is required in some instances. For example, in Case 5, it was necessary to give artificial respiration for 20 minutes. This indicated a marked fatigue of the respiratory center. The shallow respiratory movements observed in some cases after crisis is also evidence of fatigue of the center (Cases 4, 5, 8 and 9).

There is some evidence obtained by animal experimentation concerning cardiac failure which should be examined.

Early investigators in studying the effects of anoxemia on the heart and circulation found that in spite of an acceleration of the pulse rate

there was a definite lowering of the minute output of the heart (46). The acceleration of the heart beat was especially marked in sudden and severe anoxemia. Harrison and his collaborators (47) have concurred in this conclusion. They observed that the minute output was affected to a marked degree as anoxemia increased. They felt that this effect was due to the lowered oxygen tension in the heart muscle, a chemical rather than a nervous response. Resnik (48) found that anoxemia slowed conduction within the atrio-ventricular bundle and the heart muscle, and increased the sensitiveness of the sino-auricular node, thus favoring but not causing auricular and ventricular fibrillation.

While most investigators have believed that the effects of anoxemia on the heart were due to lowered oxygen tension in the myocardium, Van Liere and Crisler (49) found that vagotonic effects were produced in acute anoxemia which favored cardiac dilatation.

The effect of *pulmonary embolism* in the production of respiro-cardiac failure and on the already existent anoxemia needs a word of discussion. In the first case we encountered (Case 5) a large embolism was lodged at the point of bifurcation of the pulmonary artery in the right lung.

The question then arose as to the influence of this embolism in producing the clinical picture. The disorders of respiration and cardiac action following occlusion by embolus of the larger vessels are well known. In fact death in such instances is attributed to cardiac failure, whatever be its mechanism. As a result of experimental ligation of the pulmonary arteries, Underhill (50) found that there was a tendency for the blood to become unsaturated with oxygen and assumed that the immediate and residual symptoms of pulmonary embolism were probably due to anoxemia. This seems to be confirmed by the studies of Binger, Braw and Branch (51) who found that the tachypnea following obstruction of the larger arteries was due to anoxemia, which in turn was due to an interference with the blood flow to the lungs. They believed that cyanosis and rapid breathing after pulmonary embolism had a similar cause.

From these studies one would infer that since pulmonary embolism produces a disordered cardiac action as well as respiratory symptoms the crisis observed in patients who develop pulmonary embolism under nitrous oxide might be explained on this basis. Whether this be true or not, the existing anoxic anoxemia is certainly accentuated and this adds to its effectiveness in injuring the cerebral cortex.

The explanation of the mechanism of cerebral damage without cessation of respiratory or cardiac action is not so simple a matter.

There were four such cases in this series, three of which terminated fatally and one which recovered completely. These patients failed to regain consciousness after the anesthetic and convulsions subsequently ensued. It would seem that the clinical and pathologic phenomena are to be explained on the basis of the cumulative effect of an anoxic state sufficient to cause cerebral damage but insufficient to cause a serious respiration cardiac crisis. A lowered minute output of the heart under such circumstances would favor the slow development of a serious cortical necrosis.

*The mechanism of cerebral necrosis* In the cerebral hemispheres as in other organs of the body, the ultimate phenomenon of respiration occurs in the interchange of carbon dioxide and oxygen between the cell and the tissue fluids. As far as the nerve cell is concerned, this exchange takes place in the pericellular fluid. As for the interstitial tissues, respiration likewise occurs in the tissue fluids and in the fluid of the perivascular spaces. If this is true, the earliest lesion in cerebral anoxia would be found in the vicinity of the pericellular and perivascular spaces. That this is the case is evident from a study of the cerebral tissues. The accompanying illustration (fig 20) makes this clear. About isolated nerve cells or small groups of cells, the interstitial tissue appears vacuolated. The reduced oxygen content and oxygen tension in the pericellular fluid so injures the cell on one side and the stroma on the other that actual morphologic changes develop. A similar change may occur about small blood vessels, evidently due to a reduced oxygen supply in the fluid in the perivascular spaces (fig 21). It is this pericellular and perivascular necrosis that is ultimately responsible for the architectural and cytologic alterations in this condition. The details of these changes will be discussed in a later section.

*Summary* Should any disaster occur in the presence of an advanced anoxic state accompanying nitrous oxide-oxygen anesthesia, this state may be accentuated to a point permitting variable degrees of cerebral damage. Respiration cardiac or respiratory failure, whatever be the cause, would readily permit the development of such a dangerous stage of anoxemia. An impure gas with a high content of inert nitrogen, a defective apparatus or a mechanical obstruction of the respiratory passages may also advance the existing anoxemia to a



certain extent. What happens in a given case depends upon the oxygen saturation and tension in the arterial blood and the minute output of the heart. As yet no studies are available to indicate the average situation under nitrous oxide anesthesia, and therefore just what changes occur in the individual case can at present only be conjectured.

#### EXPERIMENTAL LESIONS OF THE BRAIN FOLLOWING DEPRIVATION OF OXYGEN

Attempts to produce cerebral lesions in experimental animals by anoxemia has not been uniformly successful. Although Martin, Loevenhart and Bunting (52) were able to produce characteristic nervous symptoms in rabbits by reducing the oxygen content of air in a respiration chamber, they report that no pathologic changes were observed in the brain and cord. In a series of experiments performed on kittens by Ford (53) the brain was found to be markedly congested after asphyxia was produced by washing out the air from a bell jar with nitrogen or by exposing the animals to carbon monoxide. In two kittens exposed to illuminating gas (impure carbon monoxide) marked symptoms were produced. The brains were studied 3 and 6 days after exposure. Chromatolysis and fatty degeneration were observed in the nerve cells of the basal ganglia and of the cortex but less marked in the latter. The swollen endothelial cells of the blood vessels contained globules of fat.

Most of the studies concerned with changes in the brain after oxygen want have been on animals which have had the carotid and vertebral arteries temporarily ligated. Ligature of these large vessels serves to deprive the brain more or less completely of its oxygen supply. The method was first introduced by Sir Astley Cooper.<sup>8</sup>

<sup>8</sup> The effect of compression of the carotid arteries has been known almost from the dawn of civilization. The Assyrians compressed these vessels in their young men to lessen the pain of circumcision. Among the Greeks the carotid arteries were called the *soporales* because of their supposed relationship to sleep. During the Middle Ages, traveling magicians used a goat as part of their stage properties. Compression of the carotids in this animal, since its cerebral blood supply is entirely dependant on these vessels, would cause it to fall helpless. Upon release the animal would jump up and run about as before. Observations of the phenomena were referred to by Morgagni and other medical writers of his time. John Bell, however, did not put much stock in these reports and made light of them. Astley Cooper produced characteristic symptoms by ligature of the vertebrals and carotids in rabbits and dogs.

Leonard Hill (54) repeated the experiments of Cooper and produced similar symptoms in the animals. In a paper with Mott (55) he described the histologic changes in the nerve cells of the cortex. A more critical study was made by Gomez and Pike (56) who noticed that the small pyramidal cells were the most sensitive to anemia. In an excellent review of the entire problem, Gildea and Cobb (57) called special attention to the areas of cortical necrosis in addition to the critical analysis of the changes in the nerve cell.

A brief enumeration of the essential principles established by experimental studies is summarized below, since it has so definite a bearing on the findings in the human brain after anoxemia.

- 1 Temporary occlusion of the carotid and vertebral arteries by ligature in animals results in convulsions, respiratory failure and permanent brain damage. Cortical changes were observed after cerebral anemia lasting from ten to fifteen minutes.

- 2 Convulsions and other symptoms may occur at once or may appear several days after circulation has been restored. In animals in which occlusion lasted eight minutes or more, spasticity, running fits, behavior peculiarities, dementia or yowling spells and blindness have been described.

- 3 In instances of mild anoxemia in animals which die immediately, only minor or poorly defined nerve cell changes were found. For the development of characteristic architectural and morphologic alterations a definite survival period is necessary.

- 4 The characteristic architectural change was the occurrence of areas of focal necrosis ("areas of devastation" of Gildea and Cobb) which required 24 hours to develop and occur predominantly within the third and fifth lamina.

- 5 A dilatation of the perineuronal and perivascular spaces occurs. The diameter of this space depends not so much on the degree of anemia as the length of survival period.

- 6 The nerve cells are predominantly affected, the large and small pyramidal cells and cells of Purkinje showing the most profound change. The varieties of nerve cell change have been described as (a) shrinking or sclerosis, (b) acute swelling, coagulation and liquification, (c) vacuolization and (d) lipoidal degeneration. Gildea and Cobb also describe (e) cells with spike like processes.

- 7 The interstitial cells were occasionally increased (perineuronal satellitosis, oligodendrogliosis and gliosis), but these changes were not common nor characteristic. Neuronophagia was occasionally observed. The perivascular microglia were also increased at times.

8 The leptomeninges were slightly thickened at times

9 The animals that died in convulsions showed dilated blood vessels. Those having a short survival period at times showed a thickening of the walls of the vessels which appeared increased in number

10 The endothelial cells of the vessels commonly contained droplets of fat

In more recent studies by Yant and his associates (58), asphyxia was produced in dogs by exposing them to carbon monoxide and to atmospheres deficient in oxygen. When asphyxia was produced either comparatively rapidly or more slowly by exposure to carbon monoxide, there was found in the brain capillary dilatation and stasis, perivascular hemorrhage and dilatation of the perivascular and perineuronal spaces. The nerve cells of the cortex, basal ganglia, cerebellum and nuclei of the medulla showed either sclerotic or acute degenerative changes. The same changes were present in the brains of dogs and rats in which asphyxia had been produced by exposure to atmospheres deficient in oxygen. When asphyxia was produced more slowly by exposures of lower concentrations of carbon monoxide and the animals sacrificed 16 to 165 days after exposure, other changes were also noted. Areas of demyelination characterized by degeneration of myelin sheaths, the formation of compound granular corpuscles, vacuolization in the affected area and the formation of small cysts filled with yellow fluid were observed. These patches of demyelination were also found in the peripheral nerves. Marked degenerative changes were also noted in the cortex as well as in the corpus striatum. The endothelial cells of the blood vessels had proliferated in the areas of hemorrhage and in the now collapsed blood vessels. The meninges had become thickened as the result of cellular proliferation.

#### CHANGES IN THE BRAIN DUE TO ANOXEMIA INCIDENT TO NITROUS OXIDE ANESTHESIA

##### *A Gross pathology*

The gross changes in the brain in anoxic states are, as one would expect, of relatively minor importance, and in most instances not characteristic enough to make a pathologic diagnosis.<sup>9</sup> If a survival

<sup>9</sup> Although it is somewhat aside from the subject of this essay, a brief reference to the effects of anoxemia on the parenchymatous organs is in order since such changes were

period of sufficient length intervenes between the cerebral insult and death, changes visible with the naked eye may be found

*Early changes* After a survival period of only a few hours or days following onset of cerebral symptoms a marked injection of the pial and cortical vessels is usually found<sup>10</sup> The arachnoid is unchanged The subarachnoid space as a rule does not contain an increased amount of fluid, and the convolutions are not particularly flattened In two cases of this series, what was thought to be small areas of softening within the cortical tissue were described by the autopsy surgeon In one case, not so thoroughly studied, no cause for this observation could be ascertained In the other, small patches of red softening in the cortex were found, presumed to be of embolic origin On cut section aside from a minor hyperemia of the cortex no gross change is usually observed If the individual has survived for 3 or more days, the superficial layers may appear granular and be soft in spite of fixation No gross alterations have been found in the white matter or basal ganglia in recent cases

*Later changes* If an interval of several weeks has elapsed between onset of characteristic symptoms and death, more definite changes may be found, particularly if a hand lens is used The arachnoid may show on close inspection a spotty thickening, particularly along

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observed in the cases in this series It has been known for some time that anoxemia has produced changes in the liver and kidney in particular, although changes in the heart, lungs and even the thyroid have been described Martin, Loewenhart and Bunting (52) found degeneration in the mid zone and central zone of the liver of rabbits exposed to a reduced oxygen supply In a study comparing the effects of nitrous oxide anesthesia to those of eclampsia, Stander (59) found moderate degenerative changes in the center of the lobules of the liver and in the renal tubules of dogs after administration of this anesthetic Fahr (60) reported three cases with serious liver damage after nitrous oxide anesthesia The liver presented a yellowish brown color and was of soft consistency Microscopically, necrosis of the liver cells and hemorrhagic extravasation was found In a recent review of the problem Franken and Miklos (61) found capillary hyperemia in the liver, kidney and spleen and necrosis of the liver These changes were believed to be due to asphyxia and not to any specific action of the gas It is likely that changes in these organs observed in patients dying after administration of nitrous oxide are the result of anoxemia incident to the anesthetic

<sup>10</sup> Congestion is evidently a generalized protective response to anoxemia or asphyxia It is probably an attempt to provide tissues with more oxygen by increasing blood volume The capillary vessels to the viscera have been shown to be dilated by Franken and Miklos (61) who studied these organs after nitrous oxide anesthesia Ford (53) and Wolff and Lennox (62) also found congestion of the pial and cortical blood vessels after experimental asphyxia

blood vessels. Areas of cortex appear yellowish and atrophic. On stripping off the leptomeninges, flakes of cortical tissue adhere to them, leaving a yellowish, roughened and granular surface. On cut section the affected cortex is found to be very much thinned and presents a yellowish streak which may occupy the width of the cortex or be confined to a narrow zone just beneath the pia mater. The superficial layer separates easily from the portion continuous with the white matter. The white substance as yet shows no grossly visible change. The lenticular nucleus will frequently show a granular central necrosis. These changes were characteristic in Case 9.

*Residual alterations.* As yet no one has described the ultimate changes in the brain following nitrous oxide anoxemia. A conception of what finally occurs, however, may be gained from a study of processes initiated in the early days and weeks of the disease. From these changes one would assume that thickening of the arachnoid with adhesions to the pia mater, generalized or localized cortical atrophy with secondary changes in the white substance associated with atrophy of the corpus striatum would ultimately result. A compensatory dilatation of the ventricles and subarachnoid space could be demonstrated before death in such instances by an encephalogram.

### *B. Architectural alterations*

The alterations in the cortex following anoxemia are found to vary considerably in the cases studied, depending upon the length of the survival period and the seriousness of the lesion. As has already been indicated, there is also considerable variation in the severity of the lesion in the various areas of the cerebral cortex in a given case, the reasons for which are not evident. There are four characteristic alterations in the cerebral cortex,—*degeneration of individual cells*, *patchy areas of necrosis* (foamy degeneration), *diffuse zonal necrosis* and *complete cortical disintegration*.

*Degeneration of individual cells.* This mild type of cortical injury is of special interest since it possibly occurs in patients who recover after cerebral manifestations in the course of nitrous oxide anesthesia. In one case of this series (Case 8) the patient died of septicemia following an anoxemic episode after nitrous oxide anesthesia. While

the cortical tissue seemed more friable than usual, there were found no architectural alterations. Here and there, however, were observed nerve cells showing characteristic sclerotic change similar to that found in the areas of necrosis in the more advanced lesions in other fatal cases. These cells were shrunken and so deeply stained that their internal structure could not be made out. The fibrillar apparatus in these cells had disintegrated into a fine granular material which more or less completely filled the cytoplasm of the cell. Vacuoles were observed at times in this mass of granules. Other cells occasionally showed minor alterations which suggested a more acute change,—swelling of the cell body, eccentricity of the nucleus and disintegration of the nucleus and vacuolization of the cytoplasm.

Certain other general changes such as loss of tigroid material in the nerve cells and acute swelling of the oligodendroglia were also found, as would be expected in the cerebral tissues of an individual dying from septicemia. Clinically, typical manifestations of cerebral anoxia had existed for several days after anesthesia, and the occurrence of a mild degree of anoxia seems a very plausible explanation of the presence of these altered cells. If this be the case, for reasons not entirely clear, certain individual cells of the brain at a given moment must be more susceptible than others to noxious influences.

*Patchy necrosis* ("Herde" of Spielmeyer, areas of devastation of Gildea and Cobb). In cases with shorter survival periods, there are to be found in the cerebral cortex and basal ganglia variously sized areas which stain poorly. Upon closer examination this pale appearance is found to be due to a decrease or absence of interstitial cellular elements, to an absence or sclerosis of persisting nerve cells, to dilatation of the perivascular and perineuronal spaces, and to the occurrence of numerous vacuolar spaces in the interstitial tissue.

In order to study the early appearances and mechanism of formation of patchy necrosis, one must carefully examine other areas of the cortex which do not appear to show any serious architectural alterations under lower magnifications. The first morphologic alteration is to be found in the vicinity of individual cells or about small groups of cells. The interstitial tissue surrounding the enlarged pericellular space presents a fenestrated, lace-like appearance. This is due to the presence of numerous vacuolar spaces which progressively decrease

in size in zones more remote from the pericellular space. The enclosed cell also shows evidence of serious damage (fig 20). These findings would indicate that the earliest damage occurs at the point of ultimate exchange of oxygen and carbon dioxide between the tissue fluid in the pericellular space on one hand and the interstitial tissue and nerve cells on the other.

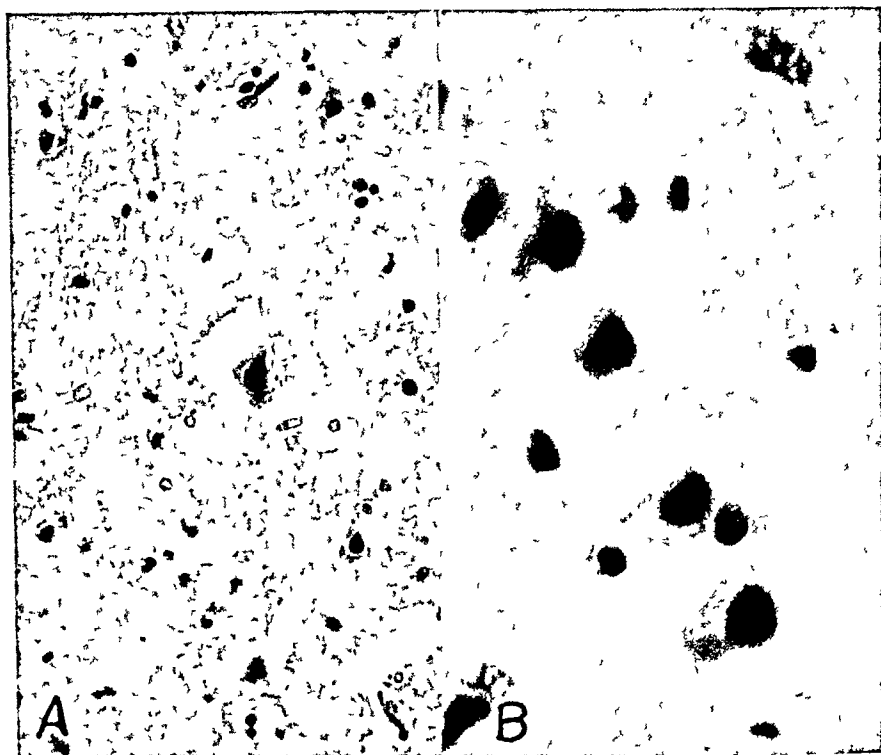


FIG 20 DETAILS OF PROCESS OF NECROSIS AS SEEN IN CASE 4. SHOWING VACUOLATED APPEARANCE OF AREA OF DEVASTATION.

Enlarged pericellular spaces are also shown. H & E  $\times 250$ . B, earliest stage of necrosis with vacuoles in interstitial tissue about group of nerve cells, H & E  $\times 620$ .

These areas of focal necrosis increase in size until a number of nerve cells are affected together with the intervening interstitial tissue. Why the process selects certain circumscribed groups of cells to the exclusion of others can only be conjectured. One might postulate that at the moment this group of cells was receiving a less abundant blood supply, and thereby soon utilized all available oxygen. It is

also possible that at some stages of catabolism the cells are more susceptible to oxygen want

By analogy one would expect that similar changes would also occur about small blood vessels. This is actually the case. In instances showing more advanced changes, circular patches of necrosis are often found about small blood vessels resembling at first sight the perivascular necrosis as observed in the liver lobule (fig 21). It is

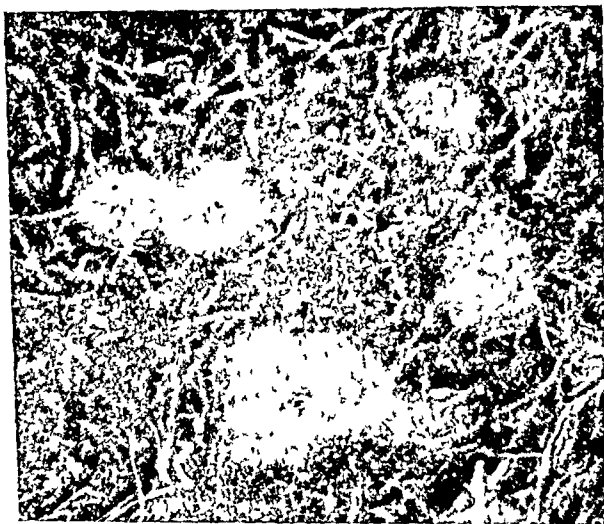


FIG 21 AREAS OF NECROSIS ABOUT BLOOD VESSELS IN CASE 4 H & E  $\times 50$

possible that patches of necrosis not so clearly related to blood vessels may actually sustain such a relationship, the level at which the section is cut in these instances having excluded the capillary

Patchy necrosis may occur as sharply circumscribed and isolated necrotic areas or as a more or less diffuse involvement resulting from confluence of a number of patches. These patches at times seem to occur as incomplete zones of necrosis and in this respect merge into the following type



*Diffuse zonal necrosis* While it is possible for a given cortical zone to be everywhere affected at the same time in more seriously damaged brains, it also is evident in others that this appearance is the result of a confluence of a number of focal areas. The irregular mottled appearance of certain regions seems to indicate that such is the case.

The same zones are not affected in all cases. In one group the superficial cellular layers (layer of small and layer of medium sized pyramidal cells) were most seriously damaged. In other cases the deep cellular layer (layer of large pyramidal cells) showed the greatest alterations. Not infrequently all layers were irregularly involved. The superficial zone (molecular layer) seemed to be least affected, perhaps because of the absence of nerve cells. The deepest layer of cells (layer of polymorphic cells) also seemed to escape the more serious effects of oxygen want. At any rate, even when three fairly distinct layers of necrosis could be identified, an incomplete intervening layer separating the zones of necrosis was usually distinguishable. In some cases (i.e., Case 2) necrosis of the deep layer seemed to be present in the form of two parallel zones which became fused over the superficial portion of the gyrus. Individual variations are probably due to the difference in cell and fiber laminations in the various parts of the cortex. It probably also depends on variations in the cortical blood supply.

*Complete cortical disintegration* This type represents the end stage of the process and is to be found only in cases with sufficiently long survival periods to permit of its development (Case 9). As the involved zones widen, the intervening zones, formed of smaller cells and particularly by transverse bands of fibers (as the bands of Bailarger), are obliterated. In this advanced stage the superficial molecular layer and the deeper polymorphic layer form the boundaries of an extensive intermediate zone of disintegration. The extent of destruction of nerve cells and fibers naturally depends upon the severity of cortical disintegration. It may be more or less complete with only fragments of nerve fibers and distorted remains of nerve cells persisting. At times incomplete rows of more or less seriously damaged nerve cells may be found on either side of the zone of necrosis.



FIG. 22 SHOWING TYPES OF NECROSIS FOUND IN LENTICULAR NUCLEUS

A, case 2 Scattered patches of necrosis  $\times 35$  B case 3 Necrosis along bundles of white fibers in the nucleus  $\times 35$  C, patches of perivascular necrosis in case 5  $\times 22$

These various types of architectural alteration have already been shown in the photomicrographs illustrating cortical changes in Cases 1 to 9

The process of cortical necrosis is accompanied by one of scar tissue formation in cases with longer survival periods. This scar, primarily the result of a vascular proliferation, is composed of a network of small blood vessels. The details of formation of this scar will be considered in a subsequent section.

Even in cases with longer survival periods, characteristic appearances of all degrees of necrosis may be found. It is, therefore, evident that any given type of necrosis may pass through all the pathologic stages. *The ultimate lesion depends upon the seriousness of the insult to that particular area during the period of anoxemia.*

In the lenticular nucleus only two of the types of degeneration can be traced (fig. 22). Focal necrosis apparently merges directly into that of more or less complete disintegration, depending upon the severity of the anoxic process.

### C Tissue and cellular change

The changes in the architectural arrangement of the cortex described above gives one a conception of the mechanism of the anoxic process. The microscopic alterations in the nerve cells on the other hand explain the ultimate pathologic picture.

1 *Changes in the nerve cells.* Since alterations in the nerve cell constitute the most important lesion from both a clinical and pathologic standpoint, this element will first be given attention. It is not a simple matter, however, sharply to separate from the standpoint of the time interval, the changes in the nerve cells from those of the stroma and its constituent elements on one hand and from those of the blood vessels and the perivascular spaces on the other. The degenerative process affects all of them coincidentally and conjointly. It may be helpful to distinguish between *morphologic changes* as demonstrated by routine methods and *structural alterations* as shown by specific ones. In order to reduce the subject to its simplest terms, both the morphologic and structural changes will be described under each type of degeneration. A number of types of cell change will be described.<sup>11</sup>

<sup>11</sup> Among the types of altered nerve cells described by Gildea and Cobb were those designated as *cells with spike-like processes*. They were found in the brains of animals that died in convulsions within an hour after arterial occlusion. In human material,

*Sclerotic change in nerve cells* (*Sklerose* (Nissl), *Zellschrumpfung* (Spielmeyer), *Shrunk* homogeneous cells (Gildea and Cobb))<sup>12</sup> This type of cellular alteration is most striking if not the most common change following cerebral anoxia. These cells may be found in early stages in the areas of focal necrosis and later at their margins. In appearance they are unmistakable. The cell body with concave lateral margins is shrunken to a variable degree within the enlarged pericellular space. This shrinkage of the cell is at the expense of the transverse diameter as indicated by Gildea and Cobb. This appearance of "sclerosis" is accentuated by the sharp outlines of the deeply-stained apical and basal dendrites which at times can be traced for some distance. The apical dendrite tends to become twisted and tortuous, assuming a cork-screw appearance. The cytoplasm of the cell stains at times a deep bluish purple color. The nucleus also shrinks and the detail of its structure ultimately becomes lost in the deepening coloration of the cell. There is a more or less universal disintegration of the neurofibrils in reduced silver preparations, which is less extensive in the Bielschowsky preparation. Granular degeneration and fragmentation of these structures were observed, the regressive change first taking place in the perinuclear region. These changes are illustrated in the accompanying drawing (fig. 23).

The fate of this type of cell is uncertain. If the involved region is profoundly damaged, complete granulation and fragmentation of

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I have failed to find many cells answering this description. In one case (Case 6, survival period 3 days 5 hours) an occasional cell with a sharp lateral spike was observed. They seemed to be variants of sclerotic cells, perhaps with their processes cut on the oblique. Cases with shorter survival periods might show these cells in greater abundance. It did not seem best to consider them as a special type in this study.

<sup>12</sup>This change in nerve cells characterized by a shrinking of the cell body and homogeneous appearance of its cytoplasm has been considered by many as essentially a chronic form of cell change. While cells of this appearance are found, to be sure, after long intervals at the margin of focal lesions (as old cortical injuries), they can also be observed within a few days after the development of a focal lesion. Gildea and Cobb found them to be invariably present after vascular occlusion, even in animals dying within a few minutes thereafter. I have found them also in cortical wounds a few days old. A more logical conclusion to reach in the light of these experiences is that sclerosis is a change not immediately fatal to the cell which may persist in a crippled form for long periods of time.

the cell results, an effect of tissue destruction *en masse*. As an individual structure, however it may persist in this form for months

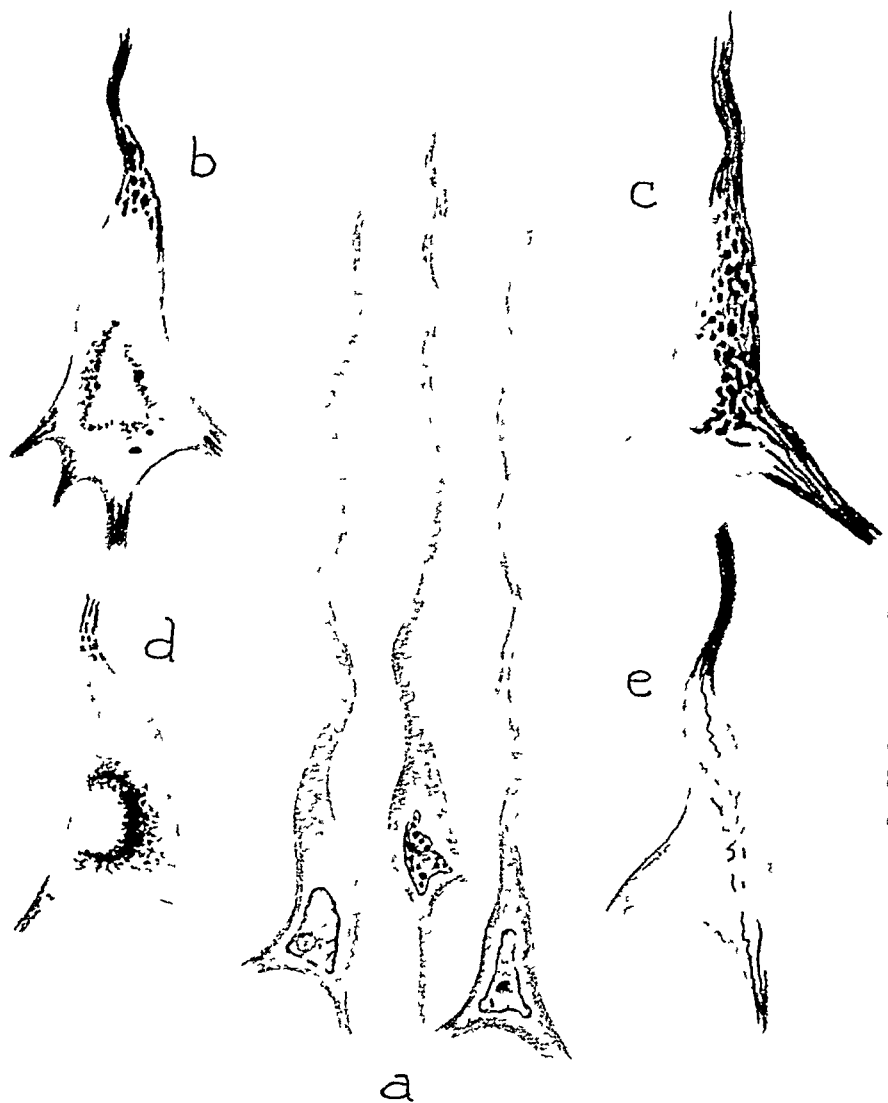


FIG 23 DETAILS OF SCLEROSSED CELLS CASE 2, SURVIVAL PERIOD 43 HOURS

*a*, group of cells showing shrunken cell bodies and tortuous apical dendrites. Cyanin method. *b*, *d*, Cajal's reduced silver preparation. *c*, *e*, Bielschowsky's silver method for neurofibrils. Showing changes in the neurofibrils in these two preparations.

and even years,—a morphologically and probably a physiologically crippled cell

Acute degeneration of nerve cells (*Schäfer's Zellerkrankung* (Nissl and Spielmeyer), Swollen cells (Gildea and Cobb)) This type of



FIG. 24. ALTERED NERVE CELLS IN CASE 6. SURVIVAL PERIOD 5 DAYS, 5 HOURS

a and f cyanin method showing condensation of tigroid material, b, neuronophagia, c, sclerotic cell, g-k, changes observed in silver carbonate preparation, g and i, mace like swellings of basilar dendrites h-j swelling of apical process

cell change is one in which the alterations are profound and undoubtedly lead to complete disintegration and death within a com-

paratively short time The cell body is swollen and rounded, its cytoplasm becoming granular and stains lightly (figs 25 and 26) The occurrence of vacuoles gives the cell a fenestrated, mesh-like appearance The tigroid granules disappear In reduced silver preparations, only a yellow rounded shadow remains At times a few

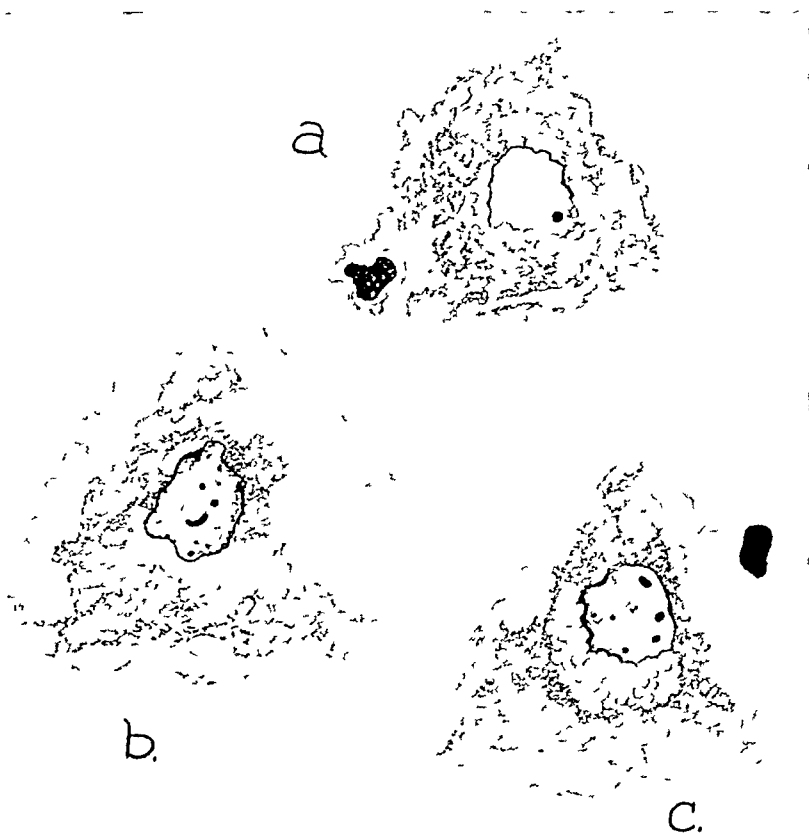


FIG 25 ACUTE NECROSIS OF NERVE CELLS IN CASE 4, SURVIVAL PERIOD 3 DAYS, 5 HOURS

C, shows acute necrosis in cell also undergoing lipoidal degeneration

peripherally placed argentophilic granules may be seen at the point of attachment of the dendrites The nuclear membrane is broken up and melts away The lightly staining chromatin material is scattered and disappears The nucleolus likewise appears faded and vacuoles may be seen in this structure before it disintegrates

*Ischemic alteration (Ischämische Zellerkrankung (Spielmeyer),*



FIG. 26 ACUTE NECROSIS OF NERVE CELLS IN CASE 1, SURVIVAL PERIOD 40 HOURS  
*a* and *b* (H & E), *c* and *d* (cyanin method) showing complete loss of tigroid substance  
*e*, *f*, and *g* (Bielschowsky method) showing degeneration of neurofibrillar apparatus and  
 collection of coarse argentophilic granules in cytoplasm



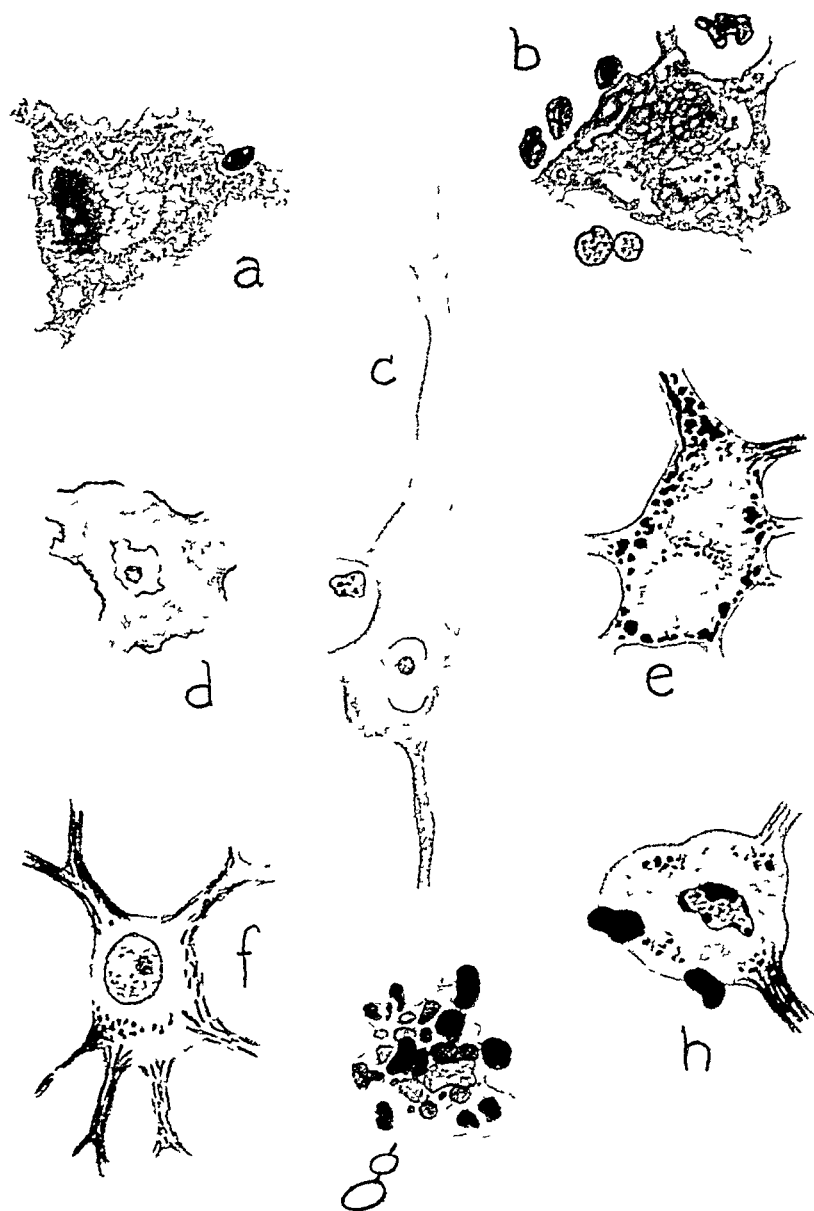


FIG. 27 CHANGES IN NERVE CELLS OF LENTICULAR NUCLEUS IN CASE 5, SURVIVAL PERIOD 4 DAYS, 7 HOURS

*a* and *b* (H & E), cytoplasm stained a brilliant pink with eosin. *a*, also shows deposit of lipoidal pigment. *c* and *d* (cyanin method) showing complete loss of tigroid substance. *e-h* (Bielschowsky method) showing disintegration of neurofibrillar apparatus.

Coagulation of nerve cells (Bielschowsky), Necrobiotic cell disorder (Jakob) This type of cell has been found in regions completely deprived of their blood supply The cell body is swollen and loses its affinity for basic stains The cytoplasm stains a bright pink color and assumes a homogeneous hyaline or ground-glass appearance The darkly-stained nucleus is shrunken and elongated It is often crowded to the periphery of the cell (fig 28, a) These cells are not so commonly observed, perhaps because the lesion is a result of a subtotal deprivation of oxygen and not of complete obstruction to the blood current

*Pigmentary atrophy* (Lipoidal pigmentation or degeneration of nerve cells) The presence of lipoidal pigment in nerve cells was observed by Gildea and Cobb in experimental cerebral lesions but they did not place particular emphasis on the observation Many of the nerve cells in human cases showed the presence of this pigment (fig 26, c and fig 28) At times the nerve cells were almost universally affected The pigment was a yellow or orange color in routine preparations and a scarlet red color when stained by Heidenhain's method The collection of pigment assumed a peri- or paranuclear situation crowding the distorted nucleus to the periphery of the cell Its formation is the result of breaking down of complex molecules into simpler ones, evidence of a disturbed metabolism It is observed ordinarily in chronic diseased states or in old age Its presence in abnormal amounts and in younger individuals is evidence of a pathologic state Oxygen want apparently favors the process

*"Calcification" (ferrugination) of nerve cells* This chronic type of alteration of nerve cells was found in but one case (Case 9) and that after an interval of 26 days The deep blue color of the nerve cells has been responsible for their designation as "calcified" cells It is now known that this appearance is due to encrustation with iron These peculiarly altered nerve cells were typically found in the dense vascular scars of the cortex and lenticular nuclei In this instance the cell body retained its characteristic morphology, but its processes were frequently sharply broken off, which gave them the appearance of being brittle The position of the nucleus was indicated by an irregular, frequently eccentric, less dense area in the deeply colored

cytoplasm No structures in the cells could be made out, their nodular margins giving one the impression of an irregular encrustation

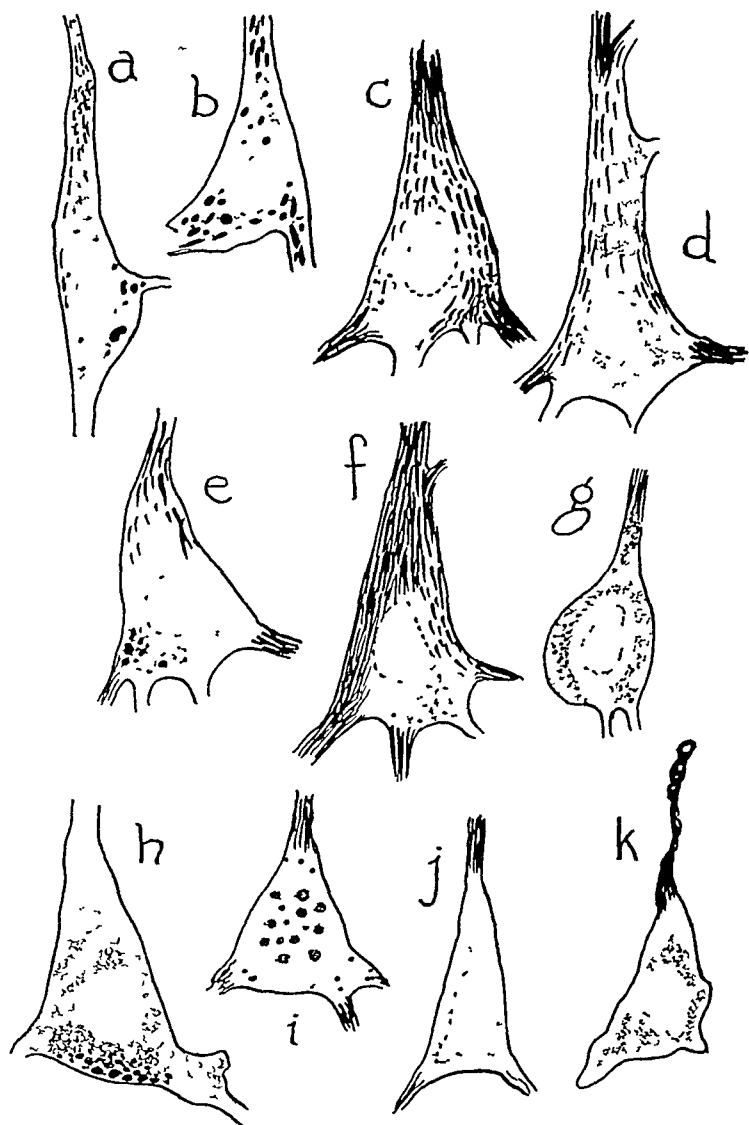


FIG 28 CHANGES IN NI UROFIBRILS AS SEEN IN BIELSCHOWSKY PREPARATIONS  
a and b, case 2 c and d, case 3 e-g, case 5 h-k, case 6

(fig 29) Prussian blue preparations showed deposits of iron in these cells

Of even greater interest than the bizarre appearance of these cells

was the presence of phagocytic cells which enclosed them. At times smaller nerve cells were found to be completely engulfed by a solitary macrophage, at others they were surrounded by several such cells attached to its cell body or to its expansions (see frontispiece). These phagocytes were stained brilliantly with eosin and contained one or more nuclei. Globules of fat were often found to be present in their cytoplasm.

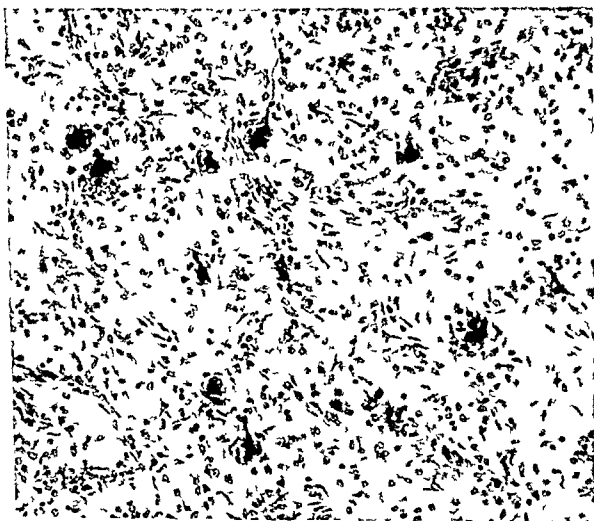


FIG. 29 'CALCIFIED' NERVE CELLS IN CASE 9, survival period 26 days. H & E.  $\times 720$

Neuronophagia and perineuronal satellitosis were occasionally observed.

*2 Changes in cells of the lenticular nucleus* The types of alterations in the nerve cells of the lenticular nucleus were for the most part identical with those in the cerebral cortex. The so-called sclerotic changes were not so characteristic, possibly due to the difference in the morphology of the cells in this structure. Lipoidal pigment was also less abundant in these cells.

3 *Changes in cells of Purkinje* The alterations occurring in the cells of Purkinje were not characteristic of anoxia, but were similar to those found in other acute conditions. The cytoplasm was more or less devoid of tigroid material and at times was vacuolated. The nucleus was occasionally eccentric and often showed disintegrative changes. The neurofibrils were almost universally fragmented and

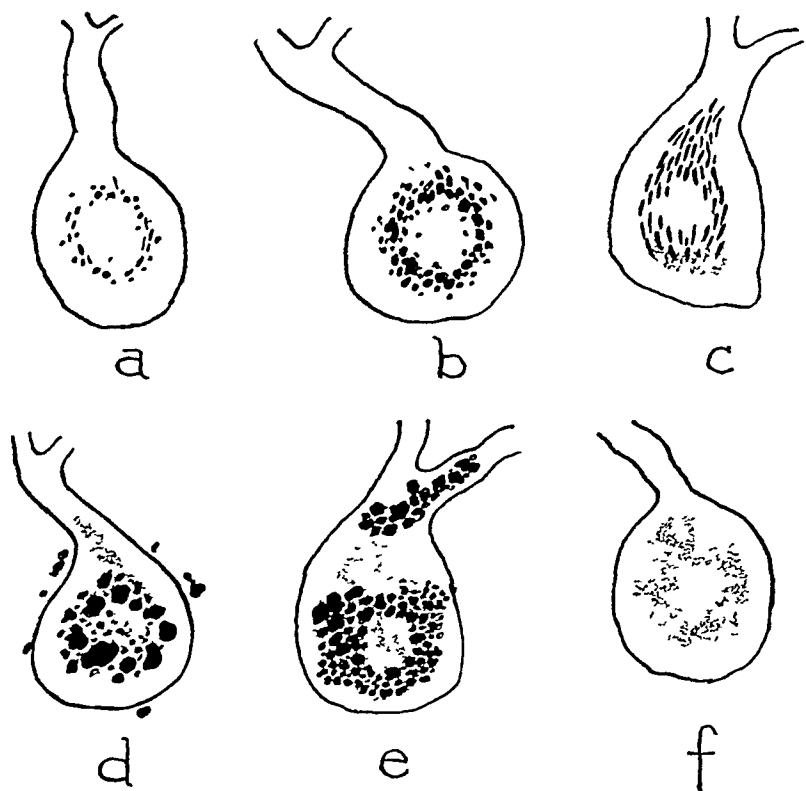


FIG. 30 CHANGES IN NEUROFIBRILS AS SEEN IN CELLS OF PURKINJE IN REDUCED SILVER PREPARATIONS

a-c, case 1 d-f, case 4 The general tendency to herudiform degeneration (clear peripheral zone) associated with coarse and fine granular degeneration is clearly shown

coarse and fine, granular necrosis and herudiform degeneration were characteristic (fig. 30)

The nerve cells of the nuclear groups in the brain stem showed remarkably little change. Often no alterations whatever could be detected.

*Changes in nerve fibers* The myelin sheaths of fibers running into

areas of cortical necrosis presented characteristic alterations, viz, swelling, vacuole formation and formation of "bulbs." Of greater interest were the changes in the axis cylinders. The finer transverse fibers were marked with small knots and rings, and at times by

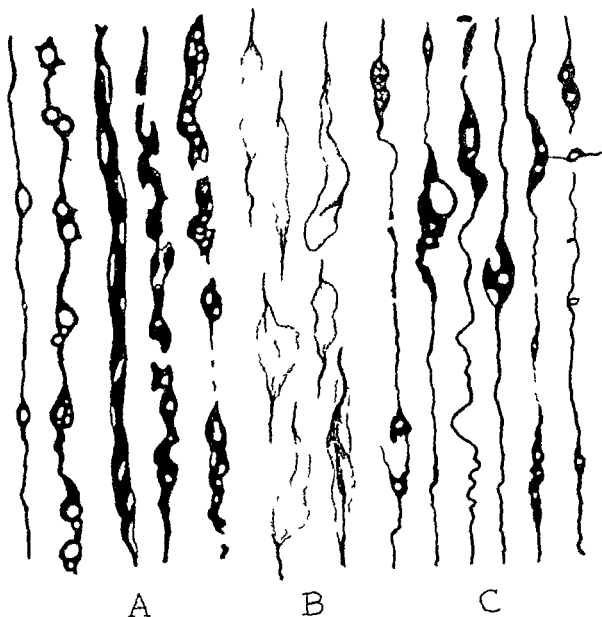


FIG. 31. CHANGES IN THE CORTICAL NERVE FIBERS

A, altered apical dendrites in case 2. B, swellings in the fine transverse fibers in case 2. C, swellings in the corticopetal fibers in case 6.

broad, leaf like expansions. The larger corticopital fibers and apical dendrites presented a great variety of appearances, as shown in the accompanying illustration (fig. 31). End-bulbs were only occasionally found and were not very characteristic.

*Changes in the leptomeninges.* Alterations in the arachnoid and pia

mater were variable and inconstant, particularly in early stages. In their series of experimental animals, Gildea and Cobb found two with thickened meninges, but attributed no significance to the observation. In the series of cases here considered, local proliferation of

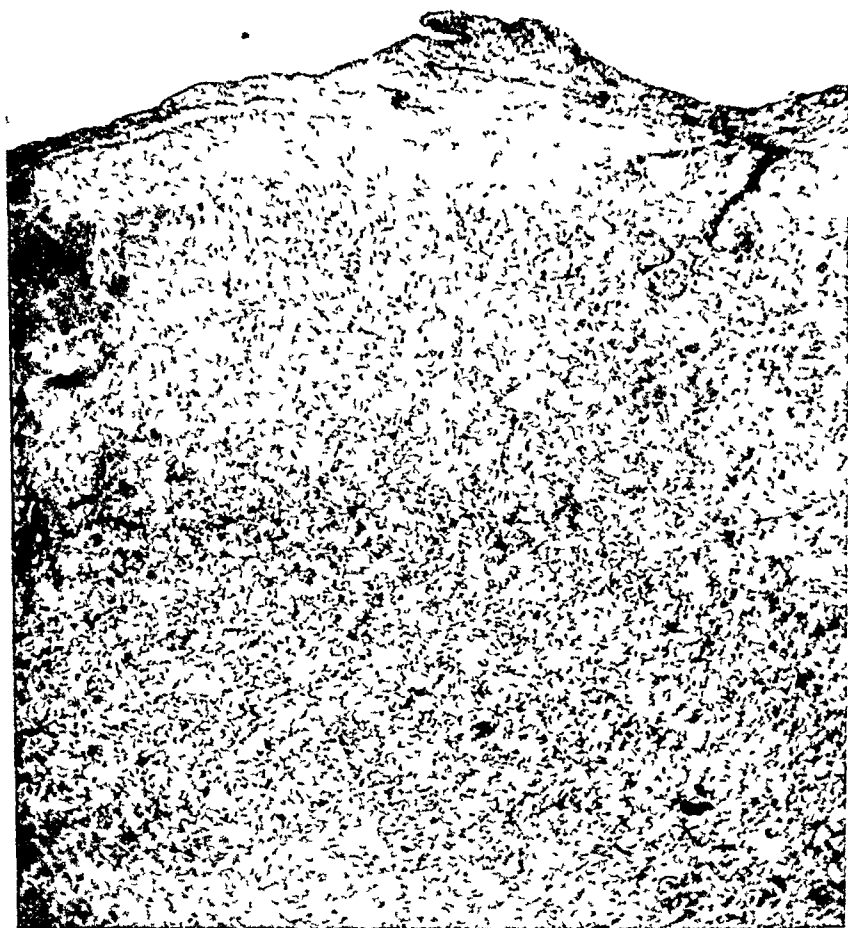


FIG. 32. LOCAL THICKENING AND ADHESIONS OF PIA TO ARACHNOID OVER DEEP CORTICAL SCAR IN CASE 9. H & E.  $\times 40$ .

arachnoidal cells was observed within the first few days. A similar change was observed at times in the pia mater, particularly about the small blood vessels. In one instance (Case 9), after an interval of 26 days, there was an advanced thickening of these membranes with formation of adhesions (fig. 32). This proliferation of cells in the

vicinity of the blood vessels suggested a disturbed tissue respiration as a possible explanation of their presence. The significance of this process is as yet not entirely appreciated.

*Changes in the interstitial cells.* The microglia showed the most active change of all the interstitial elements, a change which one would naturally expect to occur in the presence of advanced degenerative changes. Alterations in the morphology of these cells were observed within the first few days. The first intimation of cellular activity is found in routine preparations. Mitotic figures are observed in perivascular cells in superficial layers of the cortex. Since mitotic figures occur in no other type of cell in non neoplastic conditions, this indicated an active division of microglia. This was confirmed by a study of specific preparations in which active, direct and indirect division of these cells was observed. Swelling of expansions of the cell body and the occurrence of vacuoles in the processes further indicated biologic activity of these elements (fig 33). These changes were most marked in the vicinity of the areas of focal necrosis. In 3 to 5 days the cells had progressed to the "spider cell" stage, as has been found in the margin of cerebral wounds (63).

The time interval required to develop compound granular corpuscles as a result of this lesion is not known but must occur sometime between 6 and 26 days, the survival period of two of the cases. In the individual surviving for 26 days (Case 9) numerous fully developed phagocytes as well as other transitional stages were observed in zones concentric to the necrosed area (figs 34 and 35). Free fat, fragments of nerve fibers and other argentophilic material were found in these cells.

Perhaps no more interesting function of these phagocytic cells was observed than in connection with the chronically injured cells encrusted with iron observed in Case 9. These profoundly altered nerve cells were frequently engulfed by large phagocytes. The fragmented dendritic expansions often protruded from the margins of these cells. (See frontispiece.)

The *oligodendroglia* presented characteristic acute swelling in all stages of the condition. In case with longer survival periods, there was an active proliferation of these cells about the blood vessels in the subcortical white substance (fig 36).



Depending upon their locations, the *astrocytes* either underwent regressive change or were proliferated to play a part in the formation

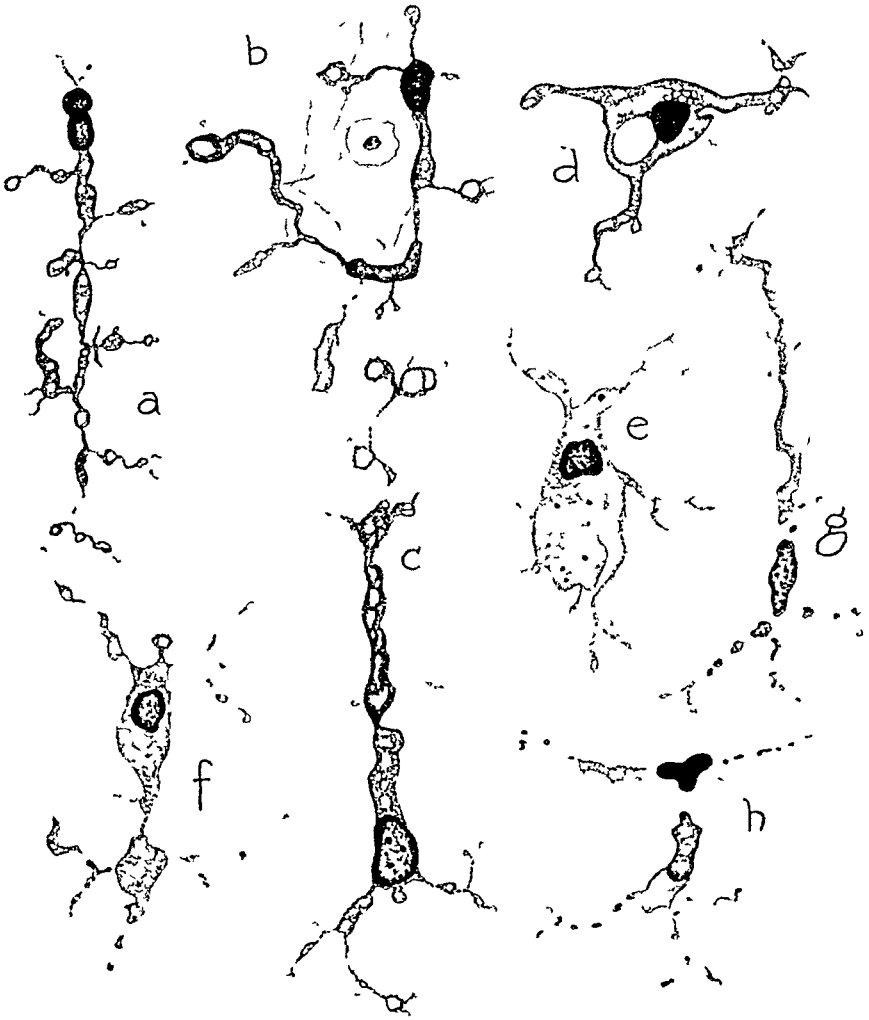


FIG 33 DRAWING SHOWING DETAILS OF EARLY CHANGES IN MICROGLIA IN CASE 1  
*a* and *c*, elongated cells (rod-cell type), *b*, alterations in perineuronal satellite, *d*, *e* and *f*, expanded forms *g* and *h*, cells undergoing disintegration

of the subsequent astro-vascular scar The neuroglia in the areas of necrosis experienced an acute regressive change along with the other

elements. The proliferative tendencies of these cells were of greater interest, however. Evidences of active cell division were not prominent in the tissues in Case 7, with a survival period of more than 6 days. On the other hand there was a definite increase in the astro-



FIG. 34. MORE ADVANCED ALTERATIONS IN MICROGLIA IN VASCULAR CORTICAL SCAR IN CASE 9. PENFIELD'S COMBINED METHOD.  $\times 300$ .

cytes at the margin of the zone of necrosis in Case 9, with a survival period of 26 days. Proliferation occurred particularly in 3 situations,—in the subpial glial layer, in the deeper layers of the cortex and the adjacent white substance beneath the zone of necrosis and about

patches of focal necrosis in the cortex itself (fig 37). In the last situation the protoplasmic cells normally present in the cortex had evidently undergone transformation into the fibrous variety

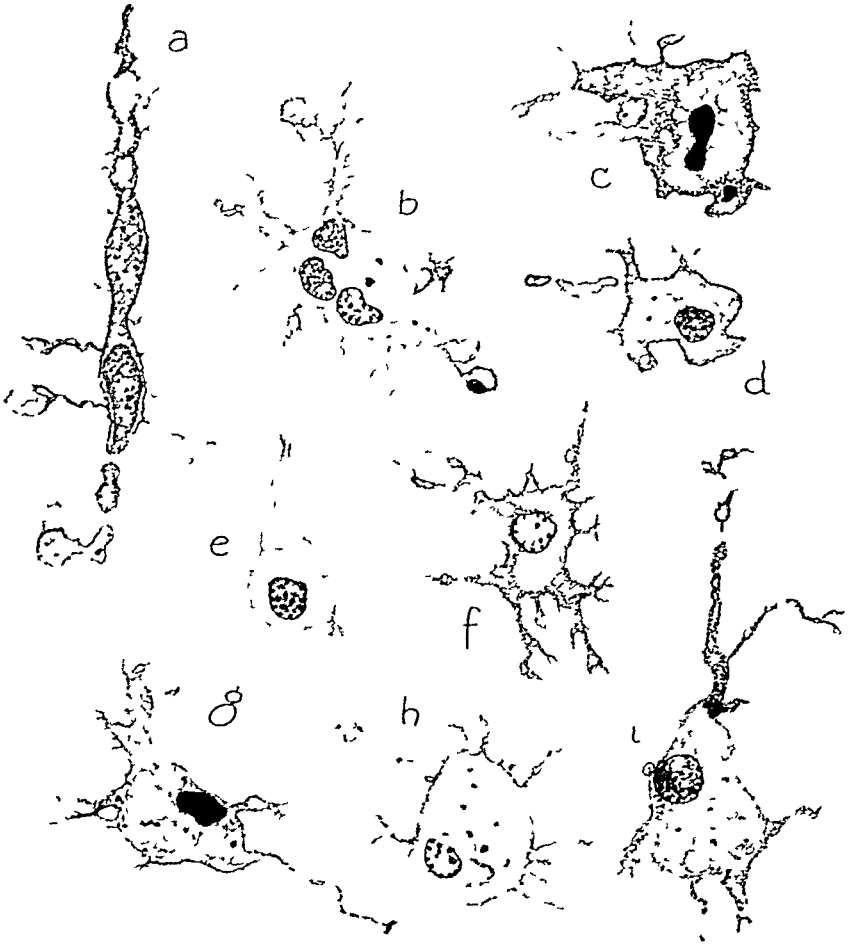


FIG 35 DRAWING SHOWING DETAILS OF MORE ADVANCED CHANGES IN MICROGLIA IN CASE 9

Vacuoles (globules of fat) and collections of argentophilic granules in the cytoplasm is shown

*Changes in the blood vessels* Aside from being the channel for carrying the oxygen-poor blood which produces the profound tissue and cellular changes, the blood vessels played a triple rôle in the resulting pathologic picture (1) by enlargement of the perivascular

spaces in giving the appearance of edema in acute stages, (2) in supplying phagocytic cells, and (3) in construction of the resulting vascular scar. The occurrence of calcareous deposits in the small blood vessels, particularly those in the lenticular nucleus, will also be mentioned.

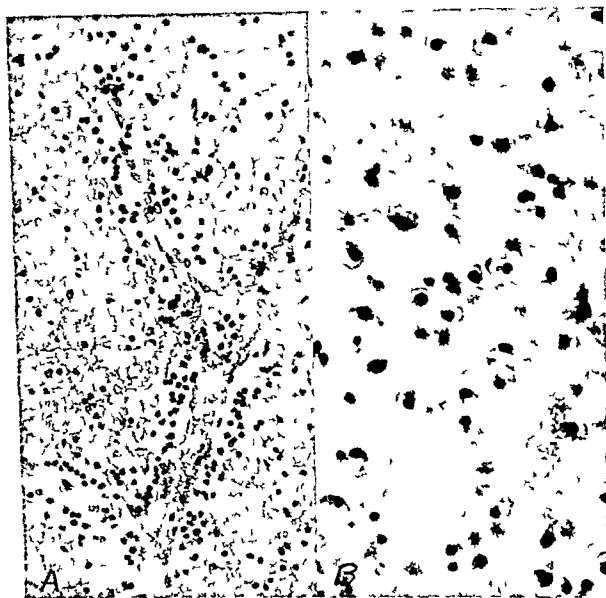


FIG. 36. CHANGES IN OLIGODENDROGLIA IN CASE 4

A, proliferation of oligodendroglia about subcortical blood vessel. H & E  $\times 180$   
B, acute swelling of oligodendroglia in white substance. Penfield's combined method,  $\times 410$

In the acute stages of the condition, the cortical tissue is found to be extremely fragile, even though it was promptly and thoroughly fixed. This fragility makes it difficult to obtain satisfactory frozen sections for metallic methods. Upon microscopic examination, the perivascular and perineuronal spaces show an increase in width, which

gives the appearance of cerebral edema. Gomez and Pike (56) found an increase in size of these spaces in experimental cerebral anemia and believed that it was an acute stage. They were as large in an animal living 16 days as in those living but a short time. In this series

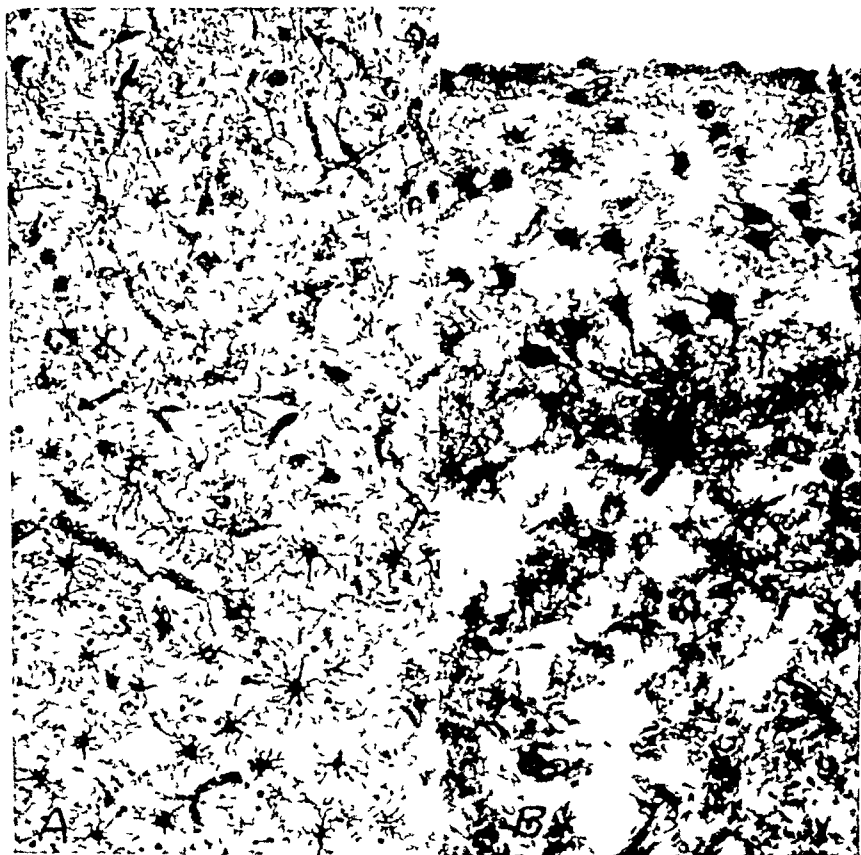


FIG. 37. ALTERATIONS IN CLASSIC NEUROGLIA IN CASE 9.

*A*, proliferation of fibrous astrocytes about vascular cortical scar.  $\times 160$ . *B*, hypertrophy and proliferation of subpial astrocytes above wide zone of cortical necrosis, visual area.  $\times 180$ . Reduced silver preparations.

of human subjects, they were variable in size in acute stages and were practically absent in one surviving 21 days.

The significance of these enlarged spaces is uncertain. Whether they indicated a true acute edema incident to an active effusion of fluid from the dilated blood vessels or whether they resulted from a shrinkage of the seriously damaged interstitial tissue and nerve cells

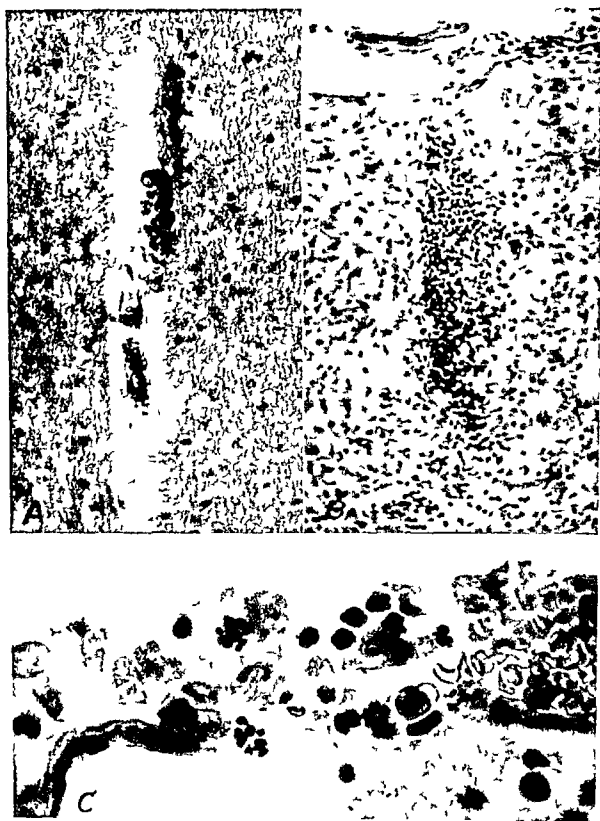


FIG 38 CHANGES IN BLOOD VESSELS

*A*, collection of fat laden phagocytes in perivascular space of subcortical blood vessel in case 3. Scarlet red stain.  $\times 240$ . *B*, perivascular round cell infiltration in cortex in case 9. H & L.  $\times 160$ . *C*, mitotic figures in walls of cortical blood vessels in case 7. H & E.  $\times 570$ .

is not known. One appearance further suggesting an active edema is the development of small vacuolar spaces in the interstitial tissues, especially about nerve cells. On the other hand the shrunken nerve cells and the compressed, deeply stained strands of the altered interstitial stroma suggests that the enlargement of the space may be passive, due to shrinkage of these adjacent elements.

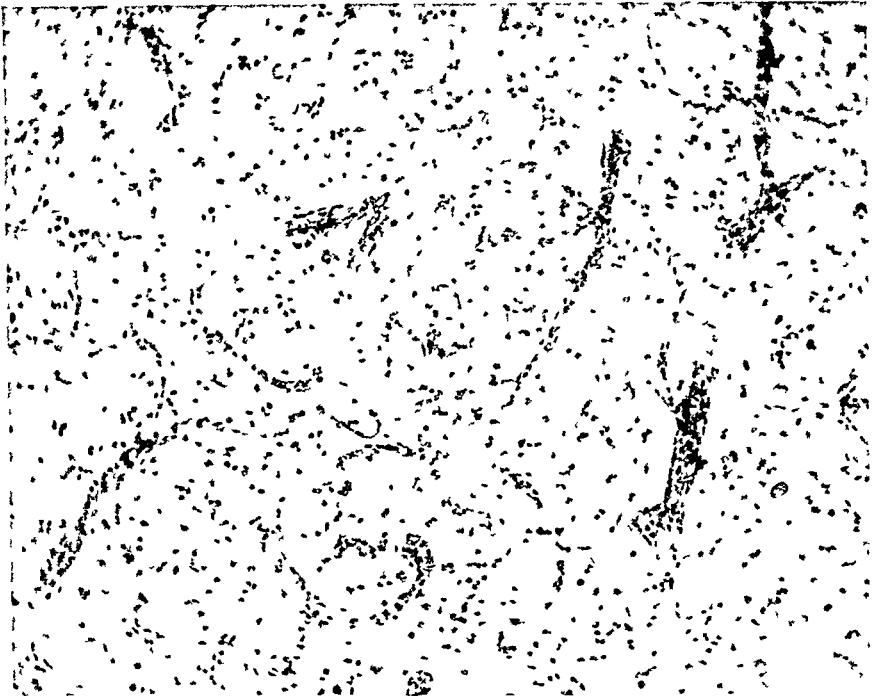


FIG. 39. PROLIFERATION OF NEW FORMED BLOOD VESSELS IN CORTEX IN CASE 7  
H & E  $\times 90$

While the blood vessels may be the source of part of the fully developed phagocytes, supplementing those of microglial origin, the greatest interest in this connection is the phagocytosis of lipoidal pigment and other material by their endothelial cells. Fat was found in the perivascular spaces and walls of the blood vessels in the experimental animals of Gildea and Cobb (57). It has also been found in similar situations in this series of cases. This lipoidal pigment, staining brilliantly with scarlet red, was observed in early stages within phagocytes in the perivascular spaces (fig. 38, a) in the blood

vessel walls and in the lining endothelial cells. This material presumably represents the disintegration of tissue lipoids and is of a similar nature to that found in the cytoplasm of the nerve cells. In later stages, when regressive changes had become more advanced, the phagocytic elements in the blood vessel walls, particularly the endothelial cells, were found to be loaded with argentophilic gran-



FIG. 40 PROLIFERATION OF BLOOD VESSELS TO FORM VASCULAR SCAR IN LENTICULAR NUCLEUS IN CASE 9, H & E.  $\times 180$

ules,—the products of degeneration of the various parenchymatous and interstitial elements.

The most conspicuous rôle played by the blood vessels was the formation of a vascular scar, which occurred only after a sufficiently long survival period. The early manifestations of proliferation were evident, however, in individuals surviving only a few days (fig. 39). In this short interval the small blood vessels in the affected areas of cortex give evidence of cellular proliferation by the constriction,



indentation or budding of the endothelial nuclei and in an actual increase in number of these elements. Mitotic figures were observed in the walls of the blood vessels in Case 7 after an interval of 6 days. At first these changes were local. As degenerative changes advanced, the small blood vessels increased in number. In Case 9, with a survival period of 26 days the scar was formed of a complex mass of small but well formed blood vessels (fig 40). The appearance of this scar has no counterpart in any other known cortical lesion.

The presence of calcareous deposits in the walls of small blood vessels of the lenticular nucleus after carbon monoxide poisoning is one characteristic of the pathologic picture. The deposit of calcium under such circumstances has been interpreted as being due to an interference or disturbance of the normal oxygen-carbon dioxide interchange through the wall of the blood vessel. The accumulated carbon dioxide unites with the soluble calcium salts in the blood plasma to form insoluble calcium carbonate. Calcareous deposits were likewise observed in the small blood vessels of the lenticular nuclei in many of the cases in this series. Their presence is probably to be accounted for on a similar basis. Calcification of the small pial blood vessels was also noted in Case 9.

#### SUMMARY

This study is concerned with the problem of cerebral asphyxia or anoxia as a result of nitrous oxide anesthesia. It is based upon clinical and pathologic observations in a series of 13 cases, 9 of which terminated fatally. In all the fatal cases an autopsy was obtained and a more or less critical examination of the cerebral tissues was made.

Cerebral manifestations following inhalation of nitrous oxide have been recognized for almost a hundred years. The immediate nervous manifestations usually consist of generalized convulsive seizures, muscular rigidity and persistent coma, at times terminating fatally with signs of "decerebrate rigidity." Delayed symptoms may occur in the form of a psychosis, a parkinsonian symptom-complex or disturbances of special sensation, particularly in the form of a partial or complete amaurosis. The patient may recover entirely after an anoxic episode, may survive for a variable period with residual

symptoms or may die within a few days. In fatal cases, death usually occurs within 2 to 7 days, but may occur only after an interval of weeks or months. Examples of each of these variations are to be found in the series of cases described herewith.

Anoxemia following administration of nitrous oxide may be the result of an impure gas, a faulty apparatus, or a preexisting or suddenly developed pulmonary lesion. The possibility of faulty administration of the anesthetic and of individual idiosyncrasy to this gas are also to be considered. Several factors may be present in a single case, all contributing to production of the cerebral lesion. Regardless of the exact source of the trouble, the clinical symptoms and the pathologic findings are the effect of *asphyxia* and are not due to any toxic effect of nitrous oxide itself.

The mechanism in most instances seems to be one of two types,—(a) sudden circulatory and/or respiratory failure with consequent cerebral damage due to the immediate utilization of the remaining small amounts of available oxygen or (b) prolonged exposure of the brain to a dangerous degree of oxygen want.

The resulting cortical lesion necessarily depends upon the degree of anoxemia and its duration. There may be (a) a sclerosis of scattered pyramidal cells, (b) an occurrence of discrete pale areas (*Herde*) in the cortex, (c) a patchy necrosis of superficial, intermediate or deep, or all cortical layers, (d) a subtotal destruction of the cortex, or if the patient survives for a sufficient interval, (e) a vascular scar may result due to the formation of new blood vessels. Changes in the nerve cells may be described as (a) sclerotic, (b) acute degenerative, (c) ischemic, and in chronic cases (d) "calcified" nerve cells. Lipoidal degeneration (e) is also a common form of cellular change. The microglia develop into compound granular corpuscles in the presence of necrosis. The astrocytes adjacent to the necrotic areas undergo proliferation to aid in the formation of the astro-vascular scar. The oligodendroglia undergo acute swelling and variable degrees of proliferation, particularly in the subcortical white substance. The arachnoid and pia may show cellular proliferation, and adhesions between these two membranes may take place.

The lenticular nucleus seems to be affected to about the same degree as the cerebral cortex, and essentially the same architectural

and cellular changes are found. Small globules of calcium are commonly observed in the small blood vessels in this structure similar to those found in carbon monoxide poisoning. The Purkinje cells of the cerebellar cortex are quite markedly altered.

A study of the brain in fatal cases discloses several interesting facts. Not all portions of the cortex are uniformly or symmetrically involved. This no doubt explains the variable clinical picture found in those cases surviving for several weeks or more. While it is possible to predicate the character of the lesion from the clinical history, one cannot always be sure of the severity of cortical damage. This is due to the great difficulty in evaluating all the possible causative factors. The earliest lesions are found about the pericellular and pericapillary spaces, which would suggest that the injury is a result of "tissue respiration,"—a disturbed carbon dioxide-oxygen exchange between the tissue fluids and the cellular elements.

This condition, hitherto not critically studied from a clinical and pathologic standpoint, demands further investigation. A careful analysis of all possible factors should be made at the time an accident occurs under nitrous oxide anesthesia to determine if possible the cause of the trouble. A detailed study of the brain should be made in every fatal case. The ultimate changes taking place in the brain after prolonged survival period are as yet unknown.

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# THE INTERRELATION OF CEREBRUM AND CEREBELLUM IN THE REGULATION OF SOMATIC AND AUTONOMIC FUNCTIONS<sup>1</sup>

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## I INTRODUCTION

When the advice of the late James Collier of London was sought concerning a case of suspected cerebellar tumor, he remarked "It is very easy to recognize a cerebellar lesion because the patient walks with his cerebral hemispheres", and on saying this Dr Collier promptly imitated the discontinuous progression movements on a broad base with head protruded forward, which so vividly characterize the locomotor activities of a human being with a mid-line cerebellar tumor. Collier's cryptic comment was based upon sound physiology—one of many instances in which clinical observation and inference have anticipated physiological analysis. It is my purpose to elucidate Collier's epigram by description of a series of physiological investigations extending over a period of eight years, in which the attempt has been made to secure more precise information concerning the relation of the cerebral hemispheres to the functional activities of the cerebellum. I propose in effect to give a log of the research, describing the principal experiments in the chronological sequence in which they were performed.

In a book on the reflex control of movement published in 1926 (41, Ch XX) the existing state of knowledge of the physiology of the cerebellum was summarized and a full account given of the early literature. The next year F M R Walshe (131, p 381) observed that I had marshalled all the relevant facts of the physiology of the brain-stem and spinal cord, but that the importance of the cortical element in cerebellar disturbance had been "completely overlooked." Under-

<sup>1</sup> Lecture read to the Harvey Society, New York City, February 20, 1936





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Connecticut*

## I INTRODUCTION

When the advice of the late James Collier of London was sought concerning a case of suspected cerebellar tumor, he remarked "It is very easy to recognize a cerebellar lesion because the patient walks with his cerebral hemispheres", and on saying this Dr Collier promptly imitated the discontinuous progression movements on a broad base with head protruded forward, which so vividly characterize the locomotor activities of a human being with a mid-line cerebellar tumor. Collier's cryptic comment was based upon sound physiology—one of many instances in which clinical observation and inference have anticipated physiological analysis. It is my purpose to elucidate Collier's epigram by description of a series of physiological investigations extending over a period of eight years, in which the attempt has been made to secure more precise information concerning the relation of the cerebral hemispheres to the functional activities of the cerebellum. I propose in effect to give a log of the research, describing the principal experiments in the chronological sequence in which they were performed.

In a book on the reflex control of movement published in 1926 (41, Ch XX) the existing state of knowledge of the physiology of the cerebellum was summarized and a full account given of the early literature. The next year F M R Walshe (131, p 381) observed that I had marshalled all the relevant facts of the physiology of the brain-stem and spinal cord, but that the importance of the cortical element in cerebellar disturbance had been "completely overlooked". Under-

<sup>1</sup> Lecture read to the Harvey Society, New York City, February 20, 1936

emphasized it had been, and in order to test the validity of Walshe's surmise, experiments were begun at Oxford in 1928 in which, after decerebellation, the cerebral hemispheres of cats, dogs and monkeys were removed, and the effects on the previously established cerebellar symptomatology analyzed (53)

## II EXPERIMENTS ESTABLISHING THAT THE CEREBRAL HEMISPHERES ARE RESPONSIBLE FOR CEREBELLAR TREMOR

The outstanding feature of the disturbances produced by removal or extensive injury of the cerebellum is a profound incoordination of volitional movement, a condition generally designated as cerebellar ataxia which is associated in its later stages with a coarse intention tremor<sup>2</sup> This was first recognized by Flourens (35) in 1824, and nearly all subsequent investigators have accepted ataxia with intention tremor as pathognomic of a cerebellar lesion. Mills and Weisenburg (95) introduced the excellent descriptive term "asynergia" to embrace the total picture of incoordination resulting from an extensive cerebellar lesion, but Holmes more recently has defined the term (63, p 479) as "the absence or disturbance of that proper synergic association in the contraction of agonists, antagonists and fixating muscles, which assures that the different components of an act follow in proper sequence, at the proper moment and are of the proper degree, so that the act is executed accurately and with the least possible expenditure of energy" This more restricted definition of asynergia is the one which has come to be generally accepted

Consideration will be given first to the time of appearance of cerebellar tremor after the cerebellum has been removed

<sup>2</sup> The jerky and intermittent character of voluntary movements in cerebellar disease is difficult to describe, and the movements have been variously designated Luciani (83), for example, termed this imperfect fusion of movement "astasia", "ataxia" and "asynergia" are more comprehensive terms, sometimes used interchangeably to describe the discontinuous, decomposed and dysmetric volitional movements of cerebellar disease Gordon Holmes' (121, 63, but see especially 64) painstaking classification of the disturbances of movement and stance in cerebellar disturbance forms the basis of modern discussion and terminology of the subject, he recognizes, among other categories of impaired function, two varieties of tremor phasic intention tremor (63, p 481), and static tremor (*e g* of head and trunk, 63, p 491), we propose to group the two together as "cerebellar tremor" Inclusion of the two types of tremor in one category seems entirely justifiable in animals since many movements of cerebellar preparations terminate in a wildly oscillating tremor, and it is often difficult to determine where the phasic tremor ends and the static tremor begins

### *1 The development of tremor following removal of the cerebellum*

In the investigation just alluded to (53) 36 cats and 5 dogs were decerebellated, and attention was focussed upon the time of appearance and rate of development of "cerebellar tremor". When the cerebellum had been cleanly removed in one piece without injury to the vestibular nuclei, the animal exhibited opisthotonoid seizures for two to three days, but tremor did not generally appear until the fourth day when the head began to oscillate (Holmes' "static tremor"), the oscillations appearing whenever the creature attempted to assume the horizontal position or to reach some objective such as food. By the end of the first week the extremities showed well-marked discontinuities of movement, and in two weeks the full blown picture of cerebellar ataxia and tremor had developed. When at rest the animal appeared essentially normal except for coarse oscillation of the head, *present when sitting up but absent when lying down*. It is significant, therefore, that in cat and dog, cerebellar tremor only appears when the animals respond to sight or smell of food, or perception of an unaccustomed sound. All this points to activity of the cerebral cortex, the more so since the ataxic manifestations are always associated with what is ordinarily termed "voluntary" effort, be it in the maintenance of a special attitude or in the initiation of movement.

If the cerebral hemispheres are responsible for the ataxic and tremulous features of cerebellar deficit, one might, in accordance with Walshe's prescient hypothesis, expect these manifestations to disappear when the cerebral hemispheres have been ablated.

### *2 Diminution of cerebral tremor after removal of one cerebral hemisphere*

If an entire cerebral hemisphere is removed from a decerebellate cat the extremities opposite to the cerebral ablation immediately assume a rigid extensor posture, the rigidity being often much more intense than that following simple decerebration. In the course of time, however, the rigidity diminishes, and simple reflex movements, which would probably be classified as "associated" (130) begin to appear. These spontaneous movements occurring on the hemiplegic side show no trace of tremor or discontinuity until late in the stage of recovery, when slight tremor may be detected, occurring simul-

er. This passes with that observable on the normal side.<sup>3</sup>  
 su. regard this late appearance of discontinuous move-  
 de. complete extremities as due to innervation from the  
 w. side, since it completely disappears when the remain-  
 sy. is removed.

## II. The decerebellate-thalamic preparation

When both hemispheres are ablated from a decerebellate  
 condition of extraordinary interest results. After a

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B  
 a cat three weeks after decerebellation  
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(16 days), cerebellar tremor as such was thus entirely absent, even though a great variety of vigorously executed spontaneous movements take place. The animals generally succumbed after several weeks to skin infections incident to their excessive activity.<sup>4</sup> The dorsal surface of the brain stem of such an animal removed at autopsy together with cerebellum and hemispheres as removed at operation are shown in figure 2. Observations on decerebellate thalamic dogs have also been made by Rademaker (104) but the cerebellum was removed after the

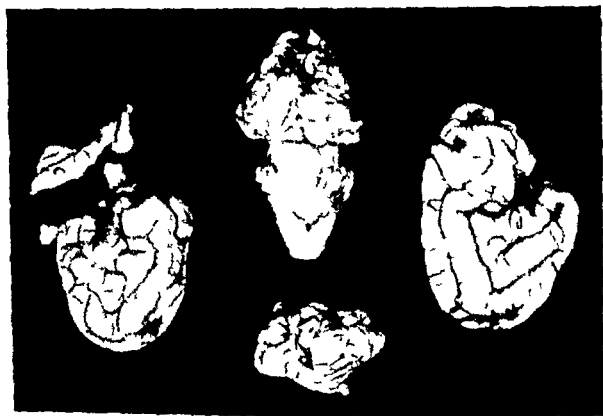


FIG. 2 THE BRAIN STEM OF THE DECEREBELLATE THALAMIC CAT SHOWN IN FIGURE 1, 1, WHICH SUCCUMBED 16 DAYS AFTER REMOVAL OF THE SECOND HEMISPHERE.

The cerebellum and cerebral hemispheres as removed at operation are also included. Note that the cerebellum has been completely removed in one piece (53).

cerebral hemispheres in his experiments so the effect on tremor could not be observed. Sager (113) has recently reported the anatomical status of one of Rademaker's decerebellate-thalamic dogs which lived 89 days.

In passing, some comment might be made about the term *asynergia* as applied to the decerebellate thalamic preparation. Unlike monkeys, cats and dogs without hemispheres have essentially normal

<sup>4</sup> The skin of these preparations was curiously prone to infection due possibly to disturbance of reflex vasomotor control of the skin.

synergic movements, but when the cerebellum is also removed, the animal sprawls horizontally and cannot stand (fig 1, *B*), it is thus gravely incoordinated (103, 53, 113), a condition which might be designated *asynergia* without tremor Rademaker's dog which lived 89 days is said to have had dysmetric movements but no tremor (113)

#### 4 *The decerebellate monkey*

Removal of the cerebellum was carried out in six monkeys and the rate of development of cerebellar tremor closely studied in four (5)<sup>5</sup> The animal attempts to execute volitional movements earlier than does

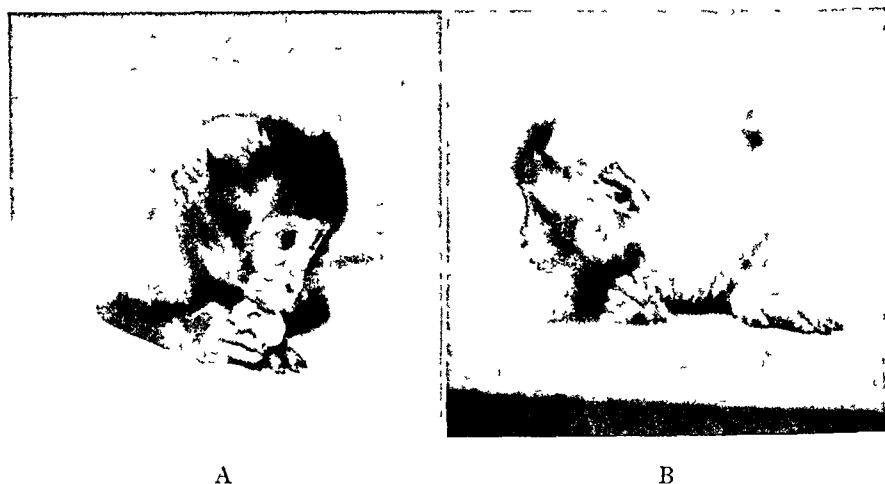


FIG 3 A A monkey two weeks after complete decerebellation showing its mode of obtaining food

B Another monkey three weeks after decerebellation showing a characteristic prone posture with inability to sit upright

the cat, in less than twenty-four hours after decerebellation a monkey usually tries to propel itself toward food, and within 48 hours the wildest ataxia of head and all four extremities becomes apparent, head tremor generally appearing first as in the cat, and the complete cerebellar picture is likely to be fully developed within two or three days

<sup>5</sup> Complete decerebellation in monkeys has been reported by Luciani (83), Munk (98), André-Thomas (3) and Rademaker (103), and extensive subtotal removal by Ferner and Turner (34), Russell (111) and Lewandowsky (81) The decerebellate chimpanzee has never been observed No one of the previous observers has devoted specific attention to the chronology of appearance of motor symptoms following decerebellation, the monkey being quite different from dog or cat

At rest, they generally lie in a prone position (figs 3, *A* and *B*) As in the cat, tremor is invariably associated with voluntary effort

Profound diminution of cerebellar symptoms follows in the monkey, as in the cat, after removal of one cerebral hemisphere This being the case, one might naturally expect that isolated removal of the motor area itself would suffice to abolish the monkey's cerebellar symptoms Experiments of this sort were carried out at Oxford in 1929-30 but with essentially negative results Indeed, ablation of the classical motor cortex from a decerebellate macaque diminished its cerebellar tremor only slightly and transiently, it quite failed to abolish it Our attention, therefore, came to be focussed upon the cerebral cortex itself, on coming to Yale in 1930 one had opportunity to study the problem in chimpanzees as well as in monkeys The last five years have accordingly been largely taken up with an analysis of cortical function in these forms, and only during the past year and a half has it seemed feasible to return to the cerebellum

### III MOTOR ACTIVITIES OF THE CEREBRAL HEMISPHERES IN MONKEYS AND CHIMPANZEES

Discussion of the part played by the cerebral cortex in causing the symptoms of cerebellar deficit presupposes some knowledge of the functional anatomy of the cortex itself Studies of cellular architecture by Meynert (94), Ramon y Cajal (105), Campbell (21), Brodmann (14), the Vogts (127, 128) and von Economo (32), established the laminar structure of the cerebrum, six principal layers being recognized, and three major functional divisions the sensory reception areas, regions of motor projection, and the association areas Speaking generally the sensory areas lie in the posterior half of the hemispheres, and the motor regions in the anterior half, but there is extensive overlapping between the two, the association areas lie scattered in the frontal, parietal and temporal lobes Each of these major divisions has been further separated into areas of discrete structure In the primate series, striking homologies exist between these areas of specific structure, the general arrangement being quite similar in monkey, chimpanzee and man (72) (See figures 4, 5 and 6) When the experiments just alluded to were commenced in 1930, it seemed probable that a systematic study of the results of regional ablation of



homologous cytoarchitectural areas in monkey and chimpanzee (and in other related primate forms) might, if adequately interpreted, throw light upon the functions of the corresponding regions of the human brain. In the discussion which follows Brodmann's (14) numerical designation of the specific regions will be followed.

The simultaneous use of monkeys and chimpanzees increases the significance of results obtained from either one alone. The substantial differences observed between these forms pointed to greater dominance of many cortical functions in chimpanzees than monkeys, such reactions as the Babinski response being present in chimpanzees and not in monkeys (46), this suggests that a correspondingly higher degree of encephalization of such functions may be present in man, and while it has made one cautious in applying results obtained from one form to explain phenomena seen in another, it has at the same time given indication of the direction in which man is likely to differ from the anthropoids.

Since the commencement of this study more than 1000 lesions have been made in some 500 monkeys, detailed typed records being preserved for each animal with day to day observations after every lesion, the 56 lesions made in 25 chimpanzees have similarly been intensively studied. Since our principal conclusions relate to the chimpanzee, the following brief comments concerning cortical areas will be based on this form. In the appendix protocols are given describing each of the chimpanzees studied.

### *1 Motor regions of discrete structure*

In considering cerebral and cerebellar interrelationships our attention is first drawn to the motor projection areas. These lie principally, but not exclusively, in the frontal lobe, other little understood motor systems have been found arising in temporal and postcentral convolutions (Mettler, 93). The following regions are the most important (figs 4, 5 and 6).

#### *Individual areas*

*Area 4*, which forms the principal part of the classical "motor area," extends from the base of the central sulcus anteriorly to a variable extent on the lateral surface of the precentral convolution (figs 4, 5 and 6). Histologically it is made up of characteristic agranular frontal cortex with the giant cells of Betz on the fifth layer (fig 7).

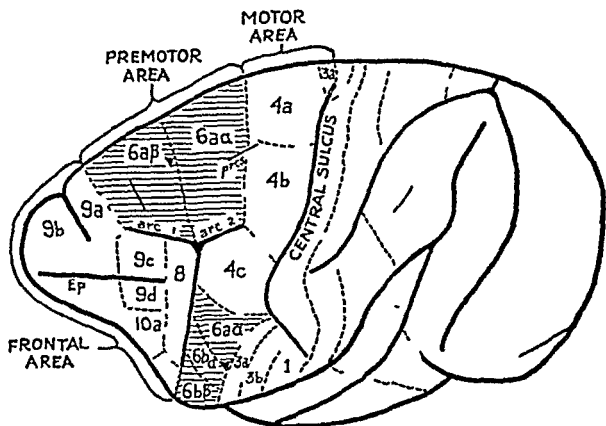
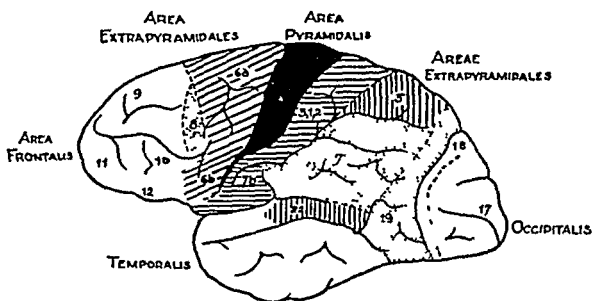


FIG 4 THE VOGT MODIFICATION OF BRODMANN'S CYTOARCHITECTURAL MAP OF THE MONKEY BRAIN

This has formed the basis of Foerster's (37) map of the human cortex in which corresponding areas have been identified, and of the present studies of the chimpanzee cortex (fig 5). The motor area is synonymous with area 4, the premotor with area 6aβ and 6aα (upper part), areas 6aα (lower part), 6bα and 6bβ have not received special designation. The eye field occupies area 8, and the frontal association areas 9, 10, 11 and 12. Areas 11 and 12 which are on the orbital surface, are not shown on the figure.



## CHIMPANZEE

FIG 5 A TENTATIVE DIAGRAM OF THE PRINCIPAL CYTOARCHITECTURAL AREAS IN THE HEMISPHERE OF A CHIMPANZEE

The principal sulci represent a schematic average drawn up by Dr Earl Walker (unpublished) on the basis of examination of 22 chimpanzee hemispheres. The margins of areas 4 and 6 are from Bucy (19). The postcentral and parietal margins are tentative being based on Ingalls (66) and on homologues with the orang hemisphere studied by Mauss (90). For the temporal lobes of the chimpanzee see Beck (8). Areas 8, 9, 10, 11 and 12 have not yet been separated in the chimpanzee.

*Area 6*, which is histologically identical with area 4 except for the absence of Betz cells, includes the electrically excitable tissue, exclusive of the eye fields, lying rostral to area 4, in recent literature the upper part of this region has been designated the "premotor area" Area 6 of the monkey has been divided by the Vogts (128) into an upper and lower part each of which has been further subdivided as indicated in the diagram (fig 4) Area 6a, upper part, is concerned with integrations affecting the extremities and viscera In man the upper part of area 6a is divided physiologically into an anterior and posterior portion  $6a\alpha$  and  $6a\beta$ , the posterior being more easily excitable electrically than the anterior part Area 6a, lower part,

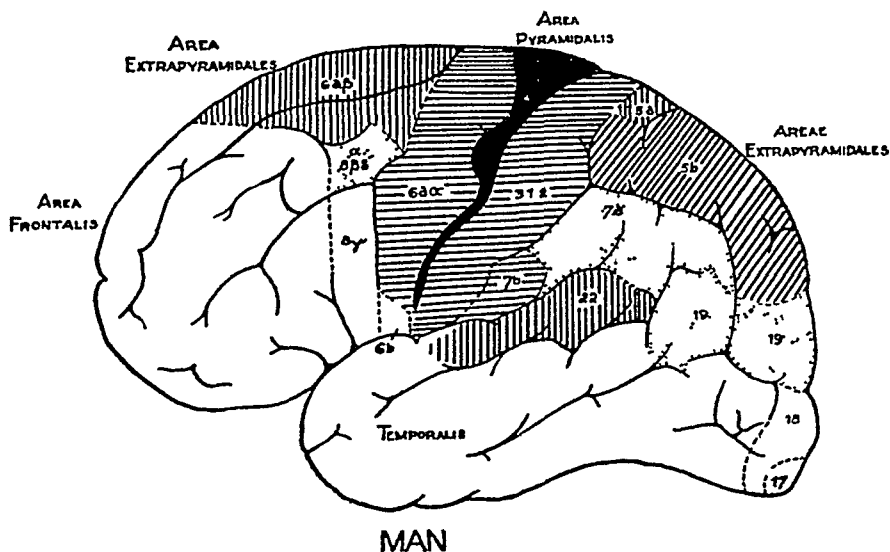


FIG 6 THE PYRAMIDAL AND EXTRAPYRAMIDAL AREAS OF A HUMAN BRAIN AFTER FOERSTER (37)

is taken up with integrations affecting the head. Area 6b is concerned with highly organized movements and with respiration

*Area 8*, the "eye field," has to do with integrations affecting the external ocular muscles and to a certain extent also with the neck muscles Recently Hines (57) has found that this area in the macaque extends to the mid-line along the strip lying rostral to area 6a as Mauss (90) found in the gibbon and orang Its position in the chimpanzee has not yet been determined cytoarchitecturally

*Areas 9, 10, 11 and 12* have been grouped together under the term "frontal association areas" This region is without motor cells in the fifth layer and its association connections are more significant than its extrapyramidal

motor projections Minkowski (96) and more recently Mettler (92), and Levin (80), following extirpation of area 9 in the macaque, have demonstrated fine fibered projections passing through the anterior limb of the

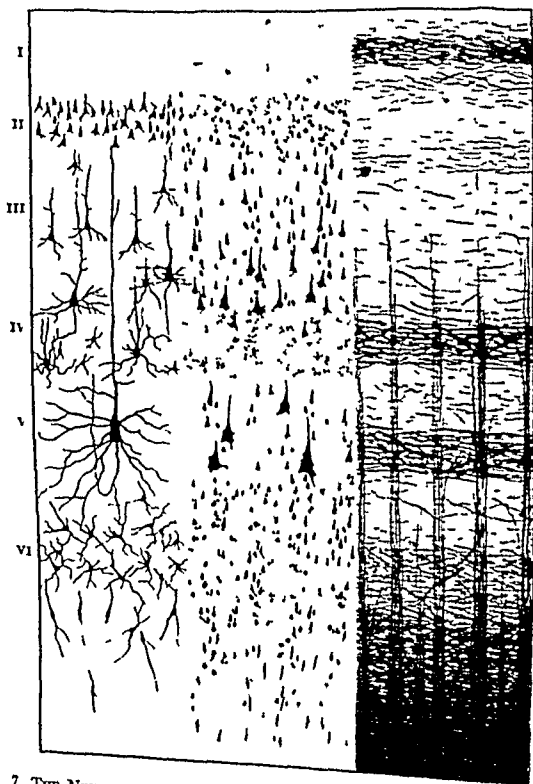


FIG 7 THE NEURONAL (LEFT), CELLULAR (MIDDLE), MYELOGENOUS (RIGHT) ARCHITECTURE OF AREA 4 IN THE HUMAN BRAIN AFTER BRODMANN AND THE VOGTS (37)

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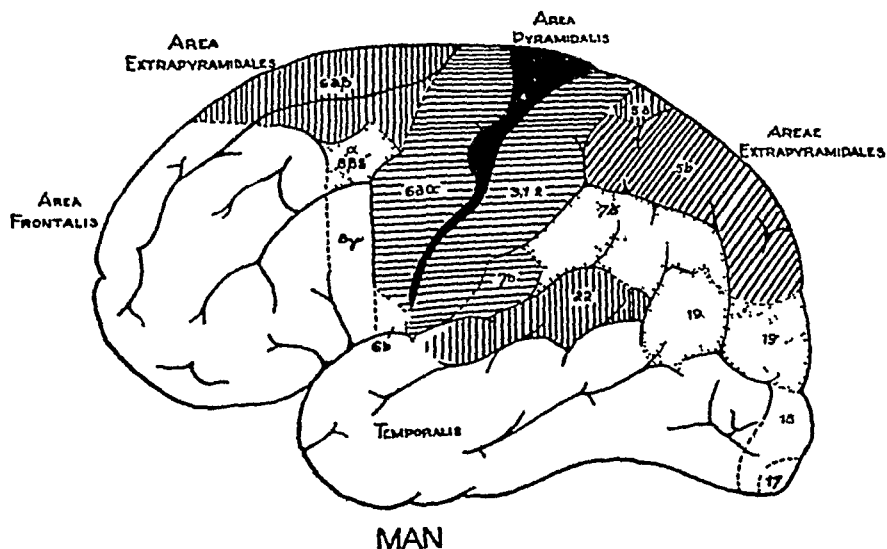


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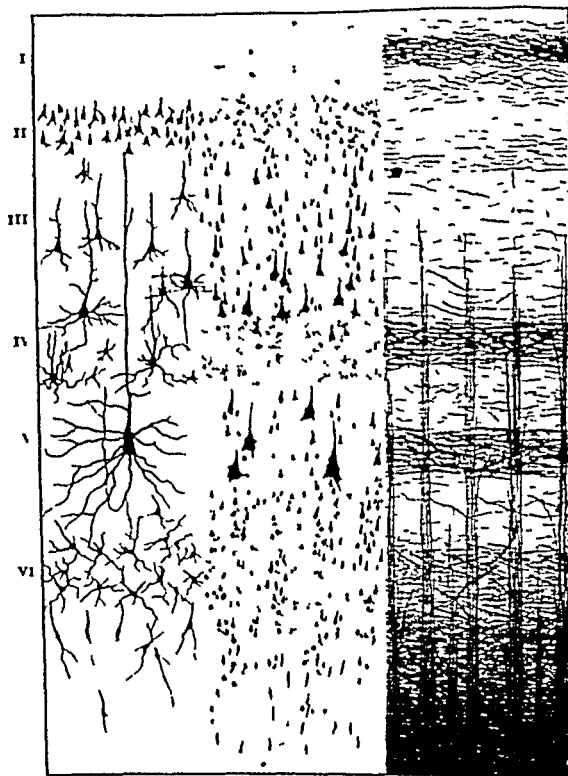


FIG. 7 THE NEURONAL (LEFT), CELLULAR (MIDDLE), MYELOGENOUS (RIGHT) ARCHITECTURE OF AREA 4 IN THE HUMAN BRAIN AFTER BRODMANN AND THE VOGTS (37)

capsule to the thalamus, caudate nucleus and pons, the principal degeneration being corticothalamic (Levin). In our experience the frontal association areas are completely inexcitable, since after areas 4, 6 and 8

have been removed, no motor response in either the somatic or autonomic spheres can be obtained, however intense the stimulation may be. The homologies of the chimpanzee frontal association areas in terms of those of the macaque are not yet clear (see 90)

*Areas 1, 2, 3 and 5* These areas constitute the postcentral and superior parietal convolutions and are stated by Mettler (93) and others, to give rise to an extensive fine-fibered projection system to subcortical regions such as the substantia nigra. Area 5 appears to give rise to a small but definite corticospinal projection (Cajal)

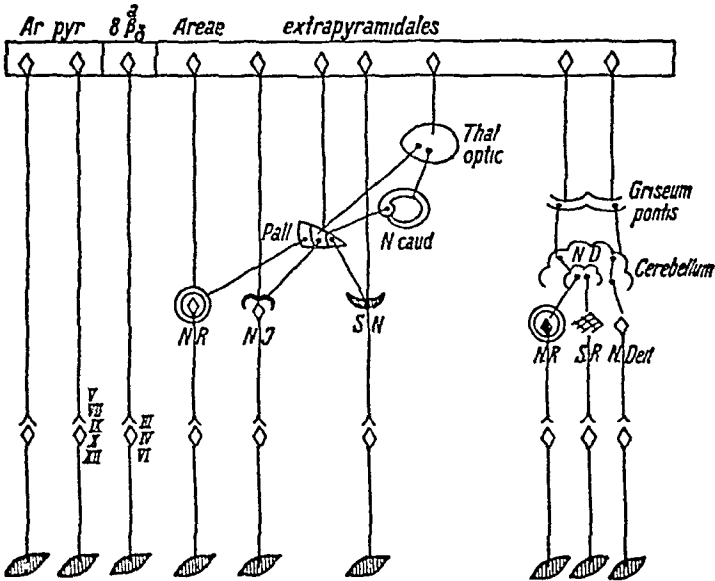


Abb 23 Schema der cortico spinalen Verbindungen

FIG 8 FOERSTER'S (37) SCHEMATIC REPRESENTATION OF THE PYRAMIDAL AND EXTRA-PYRAMIDAL PROJECTION FROM THE CEREBRAL CORTEX

*Area 22* From the posterior part of this region a subcortical motor projection takes origin which passes to the vestibular nuclei of the medulla (37, 38)

*Pyramidal and extrapyramidal projection systems* From area 4 arises the great corticospinal projection system which, since it passes through the pyramids of the medulla, has long been known as the "pyramidal tract". Extensive *extrapyramidal* projection systems also arise from areas 4 (91, 96, 80) and 6, and, behind the central sulcus, from areas 1, 2, 3, 5 and 7, and from 22. Since these extrapyramidal

motor projections are intimately associated in their functional activity with the classical extrapyramidal system of subcortical origin, it seems entirely proper, following Foerster (37, 38) and others (124, 125, 133, etc.), to designate them "extrapyramidal" motor projections from the cortex (see fig. 8). The term "parapyramidal" used by Marie and Guillain (85) is scarcely appropriate since it had reference "à côté du faisceau pyramidal sous appartenir à ce faisceau d'origine corticale".

In describing the somatic functions of these regions consideration will first be given to their electrical excitability, and then the results of regional ablation will be summarized. Autonomic functions will be considered later.

## 2. Electrical excitability of the principal areas of motor function

**Area 4.** In stimulating area 4 one must recall that it contains many structures other than the cells of Betz, *i.e.*, huge transcortical fiber systems from other parts of the cortex passing to the motor neurons, large groups of neurones, apparently receptors, in the outer laminae, and finally area 4 contributes the large extrapyramidal motor projections just mentioned. Stimulation of area 4 may call all these varied neural units into activity, and to study any unit or group of kindred units isolation is essential.

(a) *The Betz cells.* Dusser de Barenne (27, 28, 31) finds that the excitable characteristics (see 29) of area 4 are due principally to the large and giant pyramidal cells of the fifth layer. He observed that the sharply circumscribed movements normally obtainable on faradizing area 4 can still be evoked in essentially unaltered form after the outer four layers of cortex are removed by means of thermocoagulation, leaving the cell bodies of the neurones in the fifth layer undamaged. The responses after such a procedure, however, may be due in part to the extrapyramidal motor projections arising from the same cortical layer. Unfortunately these projections cannot be removed anatomically, but they can be virtually excluded pharmacologically. In 1930 Liddell, Rioch and I (52) found that certain barbituric acid derivatives gave surgical anaesthesia without abolishing excitability of the precentral convolution, and it was later found that with these anaesthetics the excitability of area 4 was preserved while that of area 6 was greatly impaired (45). When the extrapyramidal system from



area 6 was thus depressed, it is reasonable to suppose that extrapyramidal connections from area 4 are similarly impaired, since they also depend upon subcortical connections in regions specifically affected by such drugs as sodium amytal and Dial-Ciba

In such a simplified preparation, therefore, in which the outer layers of the cortex are destroyed and the extrapyramidal projections made inactive by Dial, certain characteristic responses follow monopolar faradic stimulation (Dusser de Barenne). After a brief latency discrete movements of individual muscles can be obtained similar to those with an intact motor cortex under local anaesthesia. The discreteness of response is indeed the most striking characteristic of local stimulation of the Betz cells. Continuance of the stimulus, however, may cause the response to spread to adjacent muscles, but whether the spreading is as extensive as in the normal cortex has not yet been determined. If continued indefinitely in an intact hemisphere the response may, as in a Jacksonian seizure, come to involve the musculature of the entire opposite side of the body. This spreading of a focal seizure is a well-known phenomenon clinically, and it is interesting that the "march" of the seizure from one muscle to the next appears to depend upon anatomical connections of the Betz cells existing in the deeper layers of the cortex.

(b) *Extrapyramidal projections* Attempts to study the nature of the motor influence exerted by extrapyramidal projections from area 4 (91, etc.) have also been made by many (*e g*, 119, 120), the most successful being quite recent studies of Clyde Marshall (86, 87, 88, 89) and Tower (124) in the cat, and of Tower and Hines (125) in monkey. By a retropharyngeal approach they sectioned the pyramidal pathways in the medulla as they emerge from the pons. The motor paresis sustained in the monkey<sup>6</sup> was flaccid in character, and in cat less severe than that produced by a lesion of the motor area itself (see below). The smaller muscles of the extremities were primarily affected while gross movements, especially of the proximal muscles, still remained. If the excitable frontal cortex were subsequently

<sup>6</sup> In the cat the paresis was flaccid in some positions (124) but Marshall (87) points out that flexor resistance is met when the animal is suspended in a hammock with extremities hanging pendant. Both Tower and Marshall agree that when supine (unlike a cortical rigidity (100)) the animal's extremities are completely flaccid.

removed after the pyramidal tract has been thus sectioned, there was added motor deficit affecting more particularly gross movements such as flexion at hip and knee, and the extremity became somewhat more rigid in the pendant position (Marshall, 88, Tower, 124). Stimulation of area 4, after the pyramidal tract has been cut, caused primary motor movements of a somewhat more complex type, a more intense stimulus causes an epileptiform seizure (125). Never were single muscles activated, always complex movements, often, however, generalized. *Inhibition* of resting postures was seen. Thus in an animal under light ether anaesthesia (in which clonus or spasticity may appear as a result of the anaesthetic), stimulation of area 4 will cause immediate inhibition of clonus and posture (Tower). Effects could also be demonstrated in the ipsilateral extremity. These extrapyramidal projections from area 4 are, then, capable of exerting an inhibitory effect on postural responses, and the projections furthermore can mediate certain gross types of volitional response.

*Area 6* Field 6 which is in reality a continuation, functionally and anatomically of the extrapyramidal component of area 4, is divided into several discrete regions: area 6a (upper part) generally termed the "premotor" region, area 6a (lower part) and area 6b, each of these is further subdivided as shown in figure 4. The Vogts (127, 128), Foerster (36) and Bucy (17) have shown that faradic stimulation of the premotor region yields two specific types of somatic reaction.

(a) *Area 6a (upper part)* (i) *Discrete responses* Responses of individual muscles may be obtained on stimulating the posterior portion of area 6a $\alpha$  (upper part) similar in character to those obtained from area 4. *The responses are never quite so discrete, however, as those from area 4 itself*, and there is a greater tendency to spread to adjacent muscles. These individualized responses of area 6 depend upon the integrity of area 4, for they disappear when area 4 has been removed, they disappear also when area 6 is merely separated from 4 by a superficial cortical incision between areas 4 and 6 (128, 17, see also 30). Presumably, therefore, a system of transcortical fibers arising in 6, passes superficially through the cortex to establish synaptic connection with the Betz cells. In man these discrete responses are obtained only from the posterior part of the premotor area (Foerster 36, 37, 38), the region designated by the Vogts as area 6a $\alpha$  (figs 4, 5, 6).

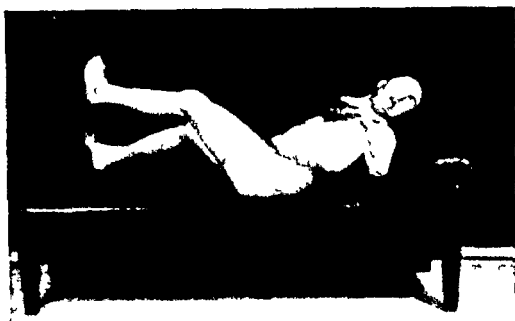
(ii). *Complex movements.* Stimulation of area 6ca, or of the posterior part 6a $\beta$ , after removal of area 4, is said to give slow, complex movements of the bodily musculature often in well-recognizable and seemingly purposeful patterns. The movements begin not with a single muscle, but generally with stereotyped movements of an entire extremity. Also a posture previously assumed, e.g., under anaesthesia, is readily inhibited from this area, especially if it happens to be extensor in type (see Tower, 124; also Riech and Rosenbluth, 100). The grasp reflex (an extensor posture) is, for example, easily inhibited from the premotor region (108). Both in man (37) and animals (17) other special synergies are seen, such as turning of the head ("adversive movement"), and torsion of trunk and pelvis. That such reactions cannot be due to spread of current is proved by the fact that they all disappear when the cortex beneath area 6a is undercut. Of localizing significance is the fact that many unilateral epileptiform seizures begin with head-turning (adversive seizures) and are followed by complex patterns of movement. Foerster's (37) remarkable photograph of a human being during an adversive seizure is shown in figure 9.

(iii) *Ipsilateral effects.* Gordon Holmes and Page May (65, p. 15 and 18) in 1908 made the passing comment that stimulation of the anterior precentral region sometimes gave ipsilateral movement of the hind limbs of the macaque. Bucy (16, 20), unaware of this observation, independently described an "ipsilateral area" around the superior lip of the superior precentral sulcus of the macaque. From this region movements of the hind limb on the same side can readily be obtained, even after the spinal cord has been semi-sectioned on the opposite side. The movements are thus due to direct innervation and not to a local segmental cross-extensor reflex.

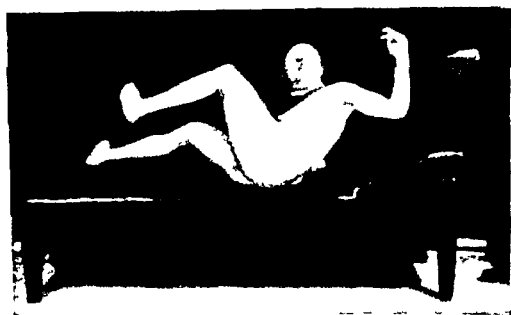
(b) *Area 6ca (lower part).* Though this region does not primarily concern us in considering cerebellar interrelationships, it is of some interest that individual movements of free, mandible and tongue can be obtained from it, as well as secondary postural movements of these muscle groups. Stimulation of the cortex abolishes the former, and undercutting destroys the latter.

(c) *Area 6ba.* In man, this small region lying anterior to the motor representation of free, tongue, glottis, etc., tends on stimulation to give rise

to sustained, and sometimes long continued movements, rhythmic and coordinated in character, of lips, tongue, mandible, pharynx and larynx, *i.e.*, chewing, licking, salivation, swallowing, mastication, croaking, grunt-



A



B

FIG. 9 IOFFSTER'S TWO REMARKABLE PHOTOGRAPHS OF AN ADVERSE SEIZURE BEGINNING WITH TURNING OF THE HEAD AND LYES TO THE SIDE OPPOSITE THE LESION AND FOLLOWED (LOWER FIGURE) BY COMPLEX MOVEMENTS OF THE SKELETAL MUSCULATURE ESPECIALLY OF THE OPPOSITE SIDE

ing accompanied by noises resembling the smacking of the lips (37). Similar observations have been made in apes by Sherrington and Grunbaum (117), and by Fulton and Dusser de Barenne (45) who observed in a spider

monkey persistent chewing and swallowing movements associated with active salivation from stimulation of this area. We have many times confirmed the observation in the course of recent studies in this laboratory and would emphasize the perserverating character of the movements once started they may continue for an almost indefinite period of time. The Vogts (128) observed that isolation of this area through incision of the cortex surrounding it does not alter the responses.

(d) *Area 6b $\beta$*  Weak stimulation in this region causes slowing and a stronger stimulus complete cessation of breathing, whether begun in the phase of inspiration or expiration. Occasionally, also, rhythmic movements of mastication are obtained in this region. This has recently been confirmed in man by Bucy (unpublished), disturbances of the breathing movements, moreover, are well-known as "aura" preceding epileptiform seizures.

Closely associated with area 6b are the responses obtained from the frontal eye fields, generally known as area 8.

*Area 8* The frontal eye field which was first accurately defined in chimpanzee by Sherrington and Grunbaum occupies a relatively small area of cortex lying just rostral to the motor face area (area 4c and area 6b), in the monkey it lies within the rostral crotch of the arcuate sulcus (figs 4 and 6), and in man and chimpanzees it forms the posterior part of the second frontal convolution. In the Vogt and Foerster maps of monkey and man, frontal eye fields are designated area 8 $\alpha\beta\delta$ .

(a) *Area 8 $\alpha\beta\delta$*  Sherrington and Grunbaum pointed out that faradic stimulation under light ether caused conjugate movements of the eyes to the opposite side. In chimpanzee, gorilla and orang, Leyton and Sherrington (82) observed that opening of the eyelid could be obtained by stimulation over a fairly wide region corresponding to area 8 $\alpha\beta\delta$ , but extending into the third frontal convolution (area 8 $\alpha$  and area 9), closure of the eyes, especially the opposite one, was also obtained regularly in certain specimens, from a point far lateral on the hemisphere. Conjugate movement of the eyes to the opposite side was commonly observed from the second frontal convolution in the region corresponding with area 8 $\alpha\beta\delta$ . Opening of the eyelids is generally associated with conjugate movements of the eyeballs. In Sherrington and Grunbaum's experience, the movements are nearly always lateral. Similar movements have been obtained from the occipital eye fields. Dilatation of the pupils was occasionally induced from area 8 $\alpha\beta\delta$ .

Foerster (36, 37) has stimulated area 8 $\alpha\beta\delta$  in man under local anaesthesia. Strong conjugate deviation of the eyes to the opposite side was observed, in a few cases upward movements, and in one case downward. The head

does not participate in the reaction and there are no visual hallucinations associated with it as in the case of occipital lobe stimulation. Epileptiform attacks have been induced in man through faradic stimulation, a seizure beginning with clonic lateral movements of the eyeballs, and in a few cases the seizure was restricted to the extraocular muscles. In general, however, it spread to the muscles controlled by area 6a $\beta$  (movement of the head to the opposite side) or to the face area. Spontaneous focal seizures beginning with the eye muscles have frequently been recorded, and in such cases lesions have been found in the frontal eye field (37).

(b) *Area 8 $\gamma$*  The most lateral parts of the frontal eye fields occupying the posterior end of the third frontal convolution in man have been designated area 8 $\gamma$  by the Vogts (128). According to these writers stimulation of area 8 $\gamma$  inhibits rhythmic movements induced by stimulation of area 6b. Thus if mastication has been induced, stimulation of area 8 $\gamma$  will inhibit the masticatory activity.

*Areas 9, 10, 11, and 12* In our experience this large region of the frontal lobe is completely inexcitable at ordinary strengths of stimulation. With very strong stimuli, eye-movements are sometimes produced with adverse movements of the head. After removal of areas 6 and 8, these movements fail to occur and in the intact animal are due undoubtedly to spread of current. Foerster states that in conscious human subjects stimulation of the prefrontal area may produce unconsciousness (37).

*Areas 1, 2, 3 and 5* Graham Brown (15) has obtained facilitation responses for excitable points in area 4, by stimulation of areas 1-2-3, but primary movements were rarely seen. This general result has been confirmed by the Vogts (128) in the cercopitheque monkey, but they insist that with strong stimuli (10 to 20 times the intensity required for area 4), discrete primary movements are sometimes obtained. Foerster (36, 38) in a detailed study of the excitability of the human cerebral cortex under local anaesthesia finds, as with area 6, that stimulation of areas 1-2-3 and 5 give rise to discrete and complex movements, the former depending upon the integrity of area 4. Sensory effects are also evoked from this region as was originally disclosed by Cushing.

*Area 22* Stimulation of area 22, especially in its posterior part, gives rise to vertigo in man, and Foerster finds that pronounced motor effects are also obtained similar to those induced from areas 1-2-3.

It is not an exaggeration to state that the human brain has been more thoroughly studied from the point of view of electrical excitability than that of the anthropoid ape Sherrington and Grunbaum (117) and Leyton and Sherrington's (82) studies were based upon some 15 anthropoids. Our series has extended to 25 chimpanzees and 4 orangs, but not all these were stimulated. Foerster, on the other hand, has stimulated nearly 200 human subjects, exploring every accessible area of the cortex faradically and galvanically, and he has meticulously correlated his findings with the known cytoarchitectural fields in man. He concluded his lectures on the motor areas of man, given in 1931, as follows (36) <sup>7</sup>

"Let me review briefly the effects of stimulating the different motor areas 4, 6a $\alpha$ , 6a $\beta$ , 8, 3-1-2, 5a, 5b, and 22. We have seen that the areas 4, 6a $\alpha$  and 3-1-2, react with single innervations of single muscle groups, of a single muscle or even a part of a single muscle. The area 8 reacts with isolated movements of the eyes. The isolated effects obtained by stimulation of the area 6a $\alpha$  and 3-1-2 are due to physiological transmission of the stimulation to area 4, i.e., they depend upon the integrity of the area 4 and its motor pathway, the pyramidal tract. So we can say that the area 4, the area pyramidalis, is the specific area for isolated innervations.

"When area 4 or the pyramidal tract is destroyed, all the other areas 6a $\beta$ , 5a, 5b, 22 (and the areas 6a $\alpha$  and 3-1-2 also) react with complex movements: eyes, head and trunk are turned to the opposite side and the contralateral extremities achieve typical complex synergies, the flexor or the extensor synergy. I call collectively all these cortical fields extra-pyramidal areas. In figure 6 the pyramidal area is represented by the black area, and the extra-pyramidal areas are hatched.

"Both groups, the pyramidal area, and the extra-pyramidal areas, cooperate when voluntary movements are performed. If area 4, the area for isolated innervations is destroyed, the pyramidal tract is interrupted, isolated movements of single segments of the extremities can no longer be performed. But voluntary mobility is by no means abolished completely. The movements which are performed under these circumstances are distinct and typical synergies.

<sup>7</sup> These lectures unfortunately were never published in detail. The above quotation is from a stenographic report of the Lecture which Prof. Foerster has kindly allowed me to quote. The material was again summarized in Foerster's Hughlings Jackson Lecture in 1935 (38).

"(1) The flexor synergy of the arm, which is observed in each severe case of spastic hemiplegia or tetraplegia, is composed of adduction of the upper arm, flexion of the forearm, pronation of the hand and flexion or extension of the fingers. These figures equally demonstrate the flexor synergy of the superior extremity.

"(2) The extensor synergy of the arm is composed of adduction of the upper arm, extension of the forearm, pronation of the hand and flexions, seldom extension, of the fingers.

"(3) The flexor synergy is combined flexion and adduction of the femur, flexion of the tibia, dorsiflexion and supination of the foot and dorsiflexion of the toes. The extensor synergy of the leg is composed of extension and adduction of the femur and flexion of the tibia and plantar flexion of the foot, the toes are flexed or extended.

"Furthermore, when in cases of destruction of the pyramidal tract a voluntary movement is to be achieved, the flexor synergy of the arm often is combined with the flexor synergy of the leg, and vice versa the extensor synergy of the arm with that of the leg. This can be well observed in hemiplegia. When the leg is flexed the arm shows the flexor synergy also and when the leg is extended the arm is extended also. In cases of spastic tetraplegia due to complete bilateral destruction of the entire pyramidal tract, all four extremities act together, whichever of the latter is moved voluntarily they are all flexed, if one single segment of one leg, for example, one foot is to be flexed, or one arm is to be flexed. They are all extended if one single segment of one arm, for example, the forearm is to be extended. These synergies performed when a single movement is to be achieved voluntarily, reveal the specific functions of the extra-pyramidal motor areas."

### *3 Regional ablation of the motor projection areas in chimpanzees*

Primary regional ablations have been made in 22 chimpanzees, 34 secondary lesions have also been studied in the same animals.<sup>8</sup> From the point of view of cerebellar function, the results obtained from lesions of the motor projection areas of the frontal lobes are of primary interest and will be described in the greatest detail, considerations of space, however, demand that only those phenomena of immediate

\* A summary of the primary ablation is given in table I and protocols concerning each animal will be found in the Appendix. Observations on 9 of these animals have already been reported from the Laboratory (see the following papers 46, 47, 77, 118, 70, 68). Others of significance will be reported in due course.



concern to cerebellar physiology be discussed. The motor area will be considered first.

*Area 4* Of the 10 cases of primary ablation of area 4a (leg representation), eight survived for three weeks or more, the longest survivals being nearly four years (see Appendix, nos. V and XI). During the first week after such a lesion the animal suffers a profound flaccid paralysis (47) but motor power returns after a variable interval, appearing first at hip, then at knee, and very much later, if at all, in the toes, *i.e.*, two to three months after the lesion. A characteristic flaccid monoplegia from area 4 lesion is shown in figure 10. The return of power is adequate to carry out such gross movements as are

TABLE I

*Summary of primary regional ablations in chimpanzee cortex (see appendix)*

	CASES STUDIED	CASES SURVIVING 3 WEEKS +	SPASTICITY		FLACCIDITY (IMMEDIATE)	BABINSKI	FORCED GRASPING, ETC	VASO-MOTOR
			Immediate	Ultimate				
Area 4 (leg)	10	8	1	0	10	8	0	0
Area 4 (arm)	1	1	0	Slight	1		0	0
Area 6	4	4	4	1	0	0	4	4
Areas 4 and 6	2	1	0	2	2	2	2	2
Areas 9-12	2	2	0	0	0	0	0	0
Areas 1, 2, 3	2	2	2	0	0	0	0	0
Area 17	1	1	0	0	0	0	0	0
Hemisphere	1	1	0	1	1	1	1	1

concerned in walking and climbing. After three to four months weak prehension usually returned in the toes, but finer movements were permanently abolished. Only one animal of the series exhibited enduring spasticity (No. IX) following an area 4 lesion, and in this instance the leg, arm and face areas were removed simultaneously.<sup>9</sup>

<sup>9</sup> Dr. Marion Hines (58) has recently made the important disclosure that enduring spasticity of the extensor muscles is produced in macaques by long narrow strip lesions involving the anterior border of area 4a and b, and extending from the cingulate to the angle of the arcuate sulcus just opposite the face area. Spasticity does not develop if shorter strip lesions are made, *e.g.*, of the anterior margin of area 4a. Since Tower and Hines (125) have found that pyramid section does not cause spasticity in the macaque, it follows that the spasticity which develops after Hines' strip lesions must be due to interruption of extra-pyramidal projections from area 4, and possibly also to interruption of transcortical projections from area 6, rather than to interruption of the pyramids themselves.

In man, following lesions of area 4a, Foerster (38), Sachs (112) and Walsh (133) have reported moderate degrees of spasticity, especially of the distal joints (toes), but Foerster (37, 38) finds that extreme spasticity in man comes only with more extensive lesions of the precentral gyrus. Following lesions of area 4a in chimpanzees the only



FIG. 10. A CHARACTERISTIC POSTURE OF THE MONOLEGIC HIND LIMB OF THE CHIMPANZEE TWO WEEKS AFTER REMOVAL OF AREA 4 FOR THE LRG (NO V)

persistent reflex changes were the Babinski and Chaddock responses (114 77, 50), the tendon reflexes may after initial depression become slightly hyperactive. Extensive atrophy of the skeletal musculature is common after area 4 lesions (No VII, Cf XIV), but not after postcentral lesions (see Fig 11). Lesions of the arm representation

(area 4b) have not been studied extensively in chimpanzees (See No XI), but in monkeys flaccidity at the elbow and shoulder is seen after ablation of area 4b, the wrist and digits may show transient spasticity (Denny-Brown, unpublished)

*Area 6* Primary ablations restricted to area 6 (see Appendix nos XII, XIII, XIV, XV) cause a striking release of tendon reflexes,

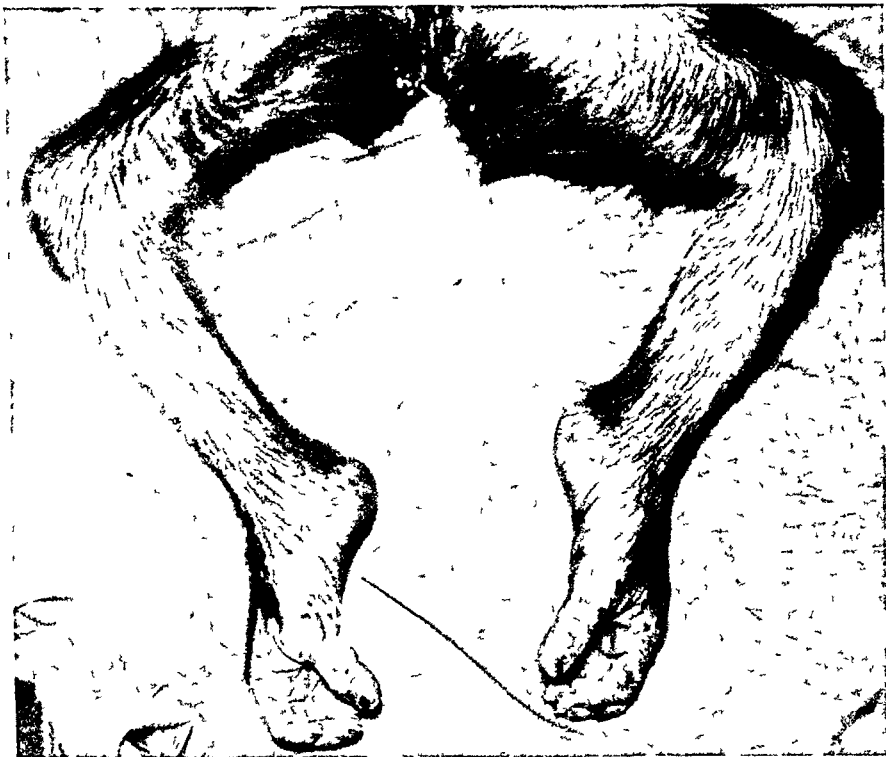


FIG. 11 SHOWING THE MARKED ATROPHY OF THE LOWER EXTREMITY AFTER A UNILATERAL LESION OF THE LEFT HEMISPHERE AFFECTING THE PREMOTOR AND MOTOR AREA OF THAT SIDE (NO XIV)

immediate spasticity, vasomotor disturbance, failure of previously acquired patterns of skilled movements and the phenomenon of forced grasping. All these symptoms, except for the disturbance of skilled movements (68) are transient, and, as with forced grasping (107, 108, 42), they recur after removing the premotor area of the opposite hemisphere (51, 47, 78). We have several recent observations suggesting that it also recurs, after section of the cerebellar peduncles

Primary regional ablations of area 6 have been studied in four chimpanzees and secondary ablations of area 6 (*i.e.*, after area 4 or some other part of the cortex has been previously removed) in six animals. The *reflex changes* are specific and striking, for in addition to forced grasping (107, 42) there is a great increase in tendon reflexes of all joints, especially in the digits (the Rossolimo, the Hoffmann, Mendel-Bechterew signs, and the fanning sign of Babinski.) A comparison of the reflex changes in lesions of area 4 with those of area 6 is shown in table II. Vasomotor disturbances which are also striking sequelae of premotor lesions will be discussed below. These reflex changes are

TABLE II

*Reflex changes following unilateral upper motor neuron lesions (cortical)*

	MOTOR (PYRAMIDAL)	PREMOTOR (EXTRA PYRAMIDAL)	COMBINED MOTOR AND PREMOTOR
Babinski	+	0	++
Chaddock	+	0	+
Spasticity	0	++	+++
Toe fanning	0	+	+
Rossolimo	0	+	++
Mendel Bechterew	0	+	++
Forced grasping	0	+	+
Hoffmann	0	+	++
Tendon	+*	++	+++
Abdominal	0	?	0
Vasomotor disturbance	0	++	++

\* Depressed or absent in early stages following a motor area lesion

evidently extrapyramidal in origin, at least the cortico-spinal fibers of area 6, though present in small numbers in the monkey (74, 60, 62), have not been found in the chimpanzee.

**Areas 4 and 6** When areas 4 and 6 are removed simultaneously (Nos XVI and XX), a flaccid paralysis supervenes for two to three days (pyramidal sign), but marked spasticity soon develops (extrapyramidal sign), and the ultimate motor paresis is far more severe than that following lesions of area 4 or area 6 alone. If area 6 is removed after area 4 as in Nos V and X (see fig 12), a previously flaccid extremity becomes immediately spastic and remains so.

**Area 8** Area 8 has been excised in several instances (unpublished)

in monkeys, transient paralysis of lateral conjugate eye movement ensued with a hemianopic disturbance of object vision. Fulton, Jacobsen and Kennard (51) observed the same phenomenon following unilateral extirpation of areas 8, 9 and 10 in monkeys, *i.e.*, for a period of 48 to 72 hours the animals were unable to carry out conjugate movement of the eye to the opposite side. In monkeys and in

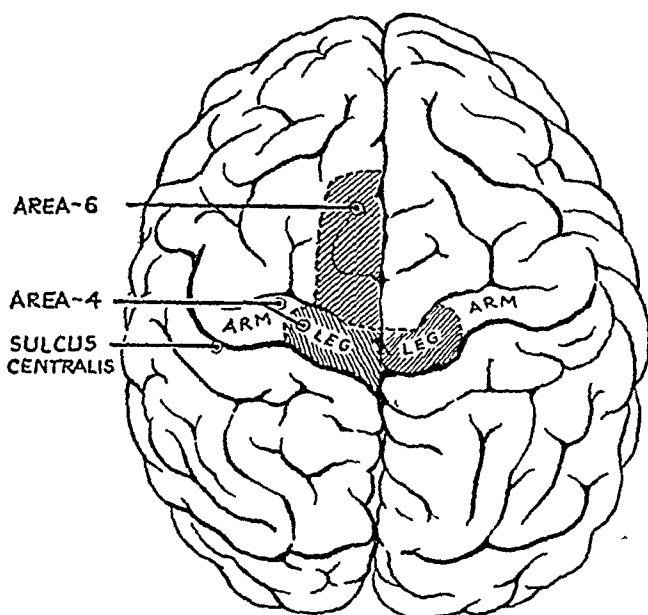


FIG. 12. A DIAGRAMMATIC REPRESENTATION OF THE CORTICAL LESIONS IN A CHIMPANZEE (No. V)

January 1st, 1932, the left leg area 4 was removed and on March 4th, 1932, the right leg area 4. After each lesion the animal sustained an enduring flaccid paralysis of the opposite hind extremity. On December 16th, 1932, the superior part of the left area 6 was removed and immediately thereafter the animal developed a strongly spastic right lower extremity which remained spastic for over two and a half years at which time the animal died.

(Foerster) the deficit, owing to bilateral innervation and superimposed projections from the occipital areas, clears rapidly and completely.

**Areas 9 to 12.** Primary regional ablations of the entire frontal association areas have been observed in two chimpanzees (Nos. XI and XVIII) and secondary regional ablations in two additional cases (see especially No. XI). In no one of these animals did reflex change occur as the result of primary regional ablation, there was no motor deficit and no change in posture or vasomotor condition of the extremities.

ties In one case of secondary ablation of areas 9 to 12, there was slight increase in tendon reflexes and augmentation of spasticity (No XI) on the side opposite to the lesion, but this may well have been due to concomitant injury to area 6 tissue which had been incompletely removed at an earlier operation In more than 30 monkeys in which regional ablations of frontal association areas have been made as a primary procedure, no reflex or postural changes were observed (see 51, 69, 70)

*Areas 1, 2, and 3* Primary removal of areas 1, 2 and 3 have been carried out in two chimpanzees (Nos XIX and XX) The animals suffered marked disturbance of motor movements in the opposite extremities with evident sensory loss, especially position sense After two or three weeks, however, they compensated in large measure for the sensory deficit, and their motor deficit also cleared, though residual awkwardness of movement remained The effects cannot be due to encroachment on area 4 for, despite the grave character of the hemiparesis during the first week after the lesion, there was no evidence of a Babinski response *The animals furthermore have not shown atrophy of their musculature*, and there was no obvious vasomotor disturbance Dr Earl Walker (unpublished) has pointed out, however, that some postural disturbance was present in the form of slight extensor spasticity of the upper extremity Similar observations have been made by T C Ruch (110) in five monkeys trained in problems of weight discrimination

*Areas 5 and 7* Primary removal of areas 5 and 7 have not been carried out, in one chimpanzee after simultaneous extirpation of areas 1, 2 and 3, simultaneous removal of 5 and 7 caused but little additional motor or postural disturbance (No XX)

*Areas 17 and 18* In one chimpanzee the whole occipital lobe was removed from one side and area 17 (*area striata*) from the opposite side (No XXII) The animal sustained no trace of motor or postural deficit or vasomotor change in the extremities as the result of the procedure

*Area 22* This region has been removed secondarily in one chimpanzee (No XIX) and no ensuent motor or postural deficit could be detected, and there was no evidence of subjective vertigo

#### 4 *Complete paralysis of volitional movements from cortical lesions*

If the primary manifestations of cerebellar lesions are caused by voluntary innervation emanating from the cerebral cortex, it becomes a problem of first importance to determine what cortical areas must be destroyed to bring about complete abolition of all volitional movement. Expressed more simply "When power returns after complete removal of the motor area, what part of the brain is responsible for taking over the functions of the ablated region?" The question has not yet been

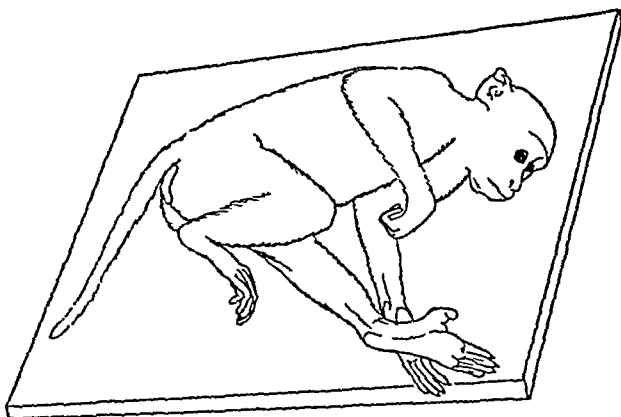


FIG 13 THE CHARACTERISTIC STEREOTYPED POSTURE OF A MONKEY FROM WHICH AREAS 4 AND 6 HAVE BEEN REMOVED FROM BOTH HEMISPHERES

Note that the undermost extremities are extended and the digits relaxed. The uppermost extremities are flexed and both exhibit forced grasping. When the animal is turned over the posture becomes reversed.

adequately answered in chimpanzees, but as far as monkey is concerned, the indications are as follows:

When area 4 has been removed, a macaque ultimately regains motor power in its extremities and, unlike the chimpanzee, may even regain the use of its digits. After several months small objects such as grains of rice can be picked up by a monkey with area 4 completely removed on both sides. If now one removes area 6a (upper part) after bilateral ablation of area 4, the animal suffers marked additional motor deficit on the side opposite to the area 6 lesion, in the course of several more months, however, the animal recovers extensively, and all four extremities may be used to some extent in voluntary movements, neck and labyrinthine reflexes are absent. If area 6a (upper part) is removed

from the remaining hemisphere of an adult animal (76), thus producing a bilateral area 4 and 6 preparation, the creature lapses into a state of profound voluntary paralysis from which, if the ablations are complete, the animal does not recover (9, 43). Such a preparation may exhibit forced grasping permanently and other stereotyped postural patterns which vary with the animal's position in space (fig. 13). The Magnus and de Kleyn reflexes, though generally present, are variable.

Such preparations, indeed, appear to be similar as far as their postural reflex status is concerned with a thalamic monkey (9, see 84). However, in the one chimpanzee which has sustained unilateral decortication (No XXV), the motor deficit and the spasticity were somewhat more intense than in the two animals (Nos XIII and XX) from which areas 4 and 6 had been removed from one side. This suggests that in the higher forms the parietal and temporal projections may play some part in postural and even in voluntary adjustments. The bilateral area 4 and 6 monkey has variable Magnus and de Kleyn reflexes, suggesting that they may be somewhat restrained by the postcentral or temporal regions.

On *a priori* grounds, then, one would expect that an animal having any part of its motor projection areas intact, especially areas 4 and 6, would exhibit cerebellar tremor.

#### IV COMBINED LESIONS OF CEREBRAL HEMISPHERES AND CEREBELLUM IN THE MONKEY

When a cerebellar syndrome is well established in a monkey and the animal has reached a steady neurological status, one may examine the effects of regional ablation of the various excitable areas of the cerebral cortex. An investigation of this character was carried out in my laboratory last year by Dr. Charles Aring. He established the cerebellar syndrome both by decerebellation, and (more frequently) by section of the peduncles on one side. Cortical ablations were then made in the opposite hemisphere. The observations may be summarized as follows (5).

##### *1 Area 4 ablation diminishes cerebellar tremor*

Since the tremor of a cerebellar lesion occurs only when voluntary movements are present, it was natural to expect that ablation of the motor area might abolish the phenomenon. However, as already men-



tioned (p 253) this proved not to be the case. If, sometime after hemi-decerebellation, area 4 was removed from the contralateral side (sparing head representation to facilitate postoperative care), cerebellar tremor was transiently abolished in the affected extremities. For several days after the motor lesion the animal exhibited a marked paresis of the contralateral extremities and used its unaffected extremities for skilled movements. The paretic limbs were first used as props, and later employed rather awkwardly in climbing and walking. With gradual return of motor power the cerebellar signs, at first abolished by the motor lesion, became more evident, but they never reached their former intensity, however, if a third lesion was made in the remaining motor area, the originally hemiparetic extremities were then used more actively, and cerebellar signs, especially tremor became conspicuous and remained so.

### *2 Bilateral motor-premotor ablation abolishes tremor*

The results of regional ablations of area 4 made it essential to determine whether cerebellar tremor could be abolished completely by a lesion restricted to the cerebral cortex. If areas 4 and 6 of one hemisphere were simultaneously removed in their entirety, cerebellar tremor was then virtually abolished for several weeks. Slight tremor eventually returned, however, as in the decorticate cat; the temporal relation of this tremor to the movements being carried out in the contralateral extremities suggested that it arose from ipsilateral cortical innervation. It was therefore evident that tremor could not be completely abolished by removal of areas 4 and 6 from one hemisphere.

In two monkeys, however, in which the motor and premotor areas were removed from both sides, cerebellar tremor was abolished for as long as the animal survived. As far as its effects on motor activities are concerned, ablation of areas 4 and 6 together appears to be equivalent to removal of an entire hemisphere. It is of some interest in passing to note that the postural status of the decerebellate bilateral area 4-and-6 monkey closely simulates that of a decerebrate monkey, except for the sluggish character of the Magnus and de Kleyn reflexes.

### *3 Isolated premotor ablations augment cerebellar tremor*

Clinical neurologists have frequently pointed out that many frontal lobe lesions may simulate lesions of the cerebellum, but it is perhaps

not so well-known that in the rare cases of cerebellar atrophy in man in which frontal lobe atrophy subsequently develop (see Demole, 26) marked accentuation occurs of all previously established cerebellar signs. In view of the diminution of cerebellar tremor with area 4 lesions, it was surprising to find that primary cortical ablations restricted to area 6, unlike those of area 4, cause a similar augmentation of cerebellar signs. In three such animals excision of the contralateral premotor area restored the neurological state present immediately after the cerebellar operation. Compensation for cerebellar deficit would appear, therefore, to be due in part at least to integrations occurring in area 6. Some compensation, to be sure, takes place in the absence of the premotor area, but this is minimal as compared with the degree of recovery observed in animals in which area 6 is intact.

If the experimental lesions were made in the opposite sequence, *i.e.*, area 6 ablation followed by section of contralateral cerebellar peduncles (three animals), the cerebellar signs following the second operation were more lasting and the compensation for the cerebellar deficit was less complete and less rapid than that following an isolated cerebellar lesion.

#### *4 Lesions of other areas*

After the establishment of a full-blown hemicerebellate picture in two monkeys (section of peduncles) simultaneous removal of areas 9, 10, 11 and 12 caused no change whatsoever in cerebellar signs. Since these areas are inexcitable electrically, it seems evident that they play no part in compensating for cerebellar deficit.

The occipital lobe has been removed from one decerebellate animal, without change in the cerebellar picture, but as yet no observations have been made on temporal or parietal extirpations in such preparations. It is probable that the parietal lobes play some part in the compensatory activities.

#### *5 Discussion*

Foerster's analysis of the excitability of the human brain together with the recent ablation studies in chimpanzees have focussed attention upon the extrapyramidal projections from the cortex. Though long recognized as anatomical entities, no serious attempt had been made prior to Foerster's work to link these projections functionally

with the extrapyramidal system of the classical neurology. The influence exerted by these projections upon the postural reflexes, together with their actual anatomical connections with the corpus striatum and the tegmental nuclei proclaim their functional unity. Indeed it would appear that just as cerebellar signs are the manifestation of imperfect compensation by the extrapyramidal areas of the cortex for cerebellar deficit, so the extrapyramidal syndromes, such as athetosis and Parkinsonism, are, by the same reasoning, to be regarded as manifestations of the inadequate compensatory activity of the cerebral hemispheres.<sup>10</sup> This idea has evidently been in the minds of Sachs (112) and others who have deliberately sacrificed part of the motor area in cases of hemiathetosis, if one were to comment upon such a procedure, it is obvious that static paralysis is less disturbing than a hyperkinetic athetosis or torsion spasm, but I venture to think that, except for such hyperkinetic syndromes, the new conception of extrapyramidal relationships will add more to a fundamental understanding of the function of the nervous system than it will to the therapy of extrapyramidal disease.

*The fronto-ponto-cerebellar system.* Thus far no mention has been made of the fronto-ponto-cerebellar system. I have deliberately avoided mentioning this anatomical pathway because so little is known concerning its site of origin. Dr Botterell has recently attempted to trace the early literature of the subject, finding that the numerous statements concerning the fronto-pontile pathway appear to go back

<sup>10</sup> A similar conception has been elaborated independently from clinical data by Kinnier Wilson (138) who after discussing choreo-athetosis remarks (p. 231) "Thus, in a definite sense, choreo-athetoid activity is the activity of cortical reflex arcs, the movements have cortical quality and yet they are involuntary."

"Over this mechanism transcortical (voluntary) inhibition has very imperfect control. It is a particular case of the general problem presented by the question of *voluntary control over an involuntarily decontrolled mechanism* (see page 250). If the views here offered can be reasonably entertained, they lead to the conception of the possibility of *involuntary cortical motor activity*—a natural development of the hypothesis I have suggested. As far at least as chorea is concerned, the conception appears to me to have much to justify it, and little less in respect to athetosis. *The spontaneous activity of choreo-athetosis, thus conceived, is nought else than a succession of cortical reflexes, high-grade movements largely comparable to those called voluntary except that the patient's volition neither initiates nor inhibits them.*"

If in this passage one substitutes "extrapyramidal" for "involuntary" the conception coincides with that just stated.

to three or four original observations—no one of them an exhaustive study. Ferner and Turner (34) in the monkey, and von Monakow (97) and Déjerine (25, pp 73, 136) in clinical cases. The clinical studies indicate that part at least of the fronto pontile connection takes origin anterior to area 4 and von Monakow's case was restricted to the second and third frontal convolutions. Several authors (von Economo, 32) state that they take origin exclusively from this region. Others have suggested that they come from the Rolandic operculum and the adjacent part of the frontal operculum (Déjerine). Actually no precise data are available concerning their origin in man and monkey. Most authors agree that the tract passes through the medial third of the crus cerebri, but Levin (80) in a recent study on the monkey, states that the fronto-pontile connection arises from both areas 4 and 6, passing to the pons via the mesial three-fifths of the crus cerebri, and a fine fibered tract from areas 9, 10, 11 and 12 passes in the most medial fifth. The recent comparative study of Abbie (1) indicates that marsupials have a fronto pontile tract (exact origin not stated) and that the monotremes have none.

A further difficulty arises in relation to the pyramidal tracts themselves. Cajal pictures Betz cell axones as bifurcating in the pons and the branches establishing synaptic connections with the pontile nuclei. Taking all the evidence together it is clear that there is an extensive extrapyramidal connection in monkeys and man, passing via the pontile nuclei through the cerebellum from both areas 4 and 6 and possibly from area 9, in addition, if Cajal's observations are given credence, area 4 establishes connection with the cerebellum through dichotomy in the pons in the fibers of the corticospinal system.

A projection from the temporal lobe also goes to the pontile nuclei (see Mettler, 93) passing on the lateral side of the crus cerebri.

*Cerebellar "hypotonia"* The problem of "hypotonia" in relation to the cerebellum also demands brief discussion. If spasticity is produced by removal of areas 4 and 6, the spastic resistance of the extremities is invariably increased on section of the cerebellar peduncles (cat and dog). In clinical and early experimental literature active discussions have occurred as to the cause of the so called "hypotonia" present after removal or extensive injury of the cerebellum (see 41, Ch XX). Recent studies in cat and dog indicate that complete

removal of the cerebellum, *if carried out without injury to the vestibular nuclei*, invariably cause an increased extensor posture of the extremities—never “hypotonia.” From this several physiologists have drawn the unjustified conclusion that clinical hypotonia so vividly described by Gordon Holmes (63) in cases of gun-shot injuries of the cerebellum must be due to vestibular injury. This conclusion does not follow from the evidence, and there are already substantial indications that a sharp distinction must be made between the functions of the two parts of the cerebellum in the higher forms, even in chimpanzee, a lesion of the cerebellar hemisphere, which in no way involves the vestibular nuclei, causes diminished resting posture of the extremities on the same side. Since the neocerebellum is probably connected intimately with the pyramidal system whose section in primates gives flaccid paralysis, I would venture the suggestion that in the higher forms interruption of the pyramidal system, or of its neocerebellar ramifications will also give rise to clinical “hypotonia”, whereas disturbance of the extrapyramidal projections or of their associated outflow from the paleo-cerebellum will give rise to augmented postures.

## V AUTONOMIC REGULATION

### 1 *The cerebral cortex*

Consideration of the functions of cerebrum and cerebellum would be incomplete without brief discussion of autonomic functions. It became obvious early in the study of regional ablations both of monkeys and chimpanzees that lesions of area 6, and occasionally those of area 4, gave rise to vasomotor disturbances which could not be accounted for on the basis of the resulting somatic paralysis. The problem clearly merited further investigation and has been analyzed both by stimulation and ablation.

*Stimulation.* Assignment of autonomic function to area 6 is new, but the fact that the cerebral cortex influences autonomic functions was disclosed within a few years of the discovery of the motor area by Fritsch and Hitzig in 1869. Almost immediately attention came to be focussed upon the visceral as well as the somatic reactions evoked on faradization of various parts of the cerebral mantle. Bechterew (7) reviewed the subject in 1911 and in a review from this Laboratory some

two hundred references to observations on the autonomic functions of the cortical areas have been collected (48)

In 1875 Schiff (115) and Danilewsky (24) independently reported changes in heart-rate and the blood pressure from stimulation of the frontal lobe of dogs. The results were confirmed by numerous investigators some of whom had used curarized animals which indicated that the changes were independent of somatic movement. The most penetrating early study, however, was that of Stricker (122) in 1886—the Stricker who first proved the independent contractility of the capillaries. After making a systematic study of the lower vasomotor centers, Stricker found that a rise of blood pressure could be obtained on stimulating the anterior part of the corpora quadrigemina. From the motor area of the cortex, he regularly obtained a rise of blood pressure which occurred after a longer latency than when the lower centers were stimulated, but he did not obtain a change in the pulse rate. From other areas Stricker observed falls in blood pressure. His experiments were well controlled and as a result of them he enunciated the view that the cortex contained vasoconstrictor as well as vasodilator representation.

Unfamiliar with these early studies, and motivated by the observation that vasomotor disturbances follow cortical ablation, E. C. Hoff and Green (61) during the past year have undertaken a series of experiments on curarized cats and monkeys. They have been able clearly to demonstrate pressor as well as depressor points on weak faradic stimulation. In the cat the pressor points are sharply circumscribed and extraordinarily responsive. Thus, rises of as much as 100 mm of mercury within two to three seconds from the onset of stimulation have been recorded. Points situated less than 2 to 3 mm from the pressor points have given falls of blood pressure. On applying nupercaine to the active points the response failed, but on plunging the electrodes into the cortical substances several millimeters the responses again appeared, indicating its cortical origin. The reflex rises of blood pressure from stimulation of the dura itself are much slower to develop and far less in magnitude than those from the pressor points. Changes of heart-rate have generally not been observed until after the rise of pressure has recurred, in which case it is attributable to a depressor reflex. However, when the stellate ganglia are first removed, cortical

stimulation may cause a direct fall in pulse rate and when the vagi have been sectioned, the stellate remaining intact, certain points appear to give increase in pulse rate. Further analysis of the problem from the point of view of precise localization, particularly in the monkey are being continued, and as far as the monkey is concerned, the principal responses are obtained from area 6.

Other aspects of cortical autonomic regulation have been investigated by stimulation but it will be impossible here to review them in detail. Sheehan (116) has found that peristalsis in the stomach of a recently fed animal can be readily inhibited by cortical stimulation, and Watts and Fulton (136) have observed increase in peristalsis in the small intestines of monkeys from cortical stimulation (see 134 and 135). Salivation can be produced from area 6a (lower part) and changes in respiration from area 6b. Contractions of the uterus were produced by Bechterew (7) and parasympathetic changes in penis and vagina.

*Ablation* The first observers to record the existence of autonomic disturbances with cortical lesions were the clinical neurologists of the last century. Chevallier (23), Nothnagel (99), Hughlings Jackson (67) and Gowers (55) reported *vasomotor* changes in hemiplegic extremities. Jackson, moreover, had observed such changes in purely cortical lesions. In his account of such disturbances Gowers was careful to point out that they were of a fluctuating character, the paralyzed extremities generally being warmer than the normal extremity during the first months after a hemiplegia, and then gradually becoming cooler (see Weiss and Ellis, 137). The fluctuating character of these disturbances has again been emphasized recently by Carmichael and his coworkers (123, 126) but despite their painstaking observations of the phenomena they have failed to elucidate the nature of the disturbance. Périssou (101), a French neurologist, attempted to correlate vasomotor disturbance with the character of the paresis, *i.e.*, he believed that the spastic hemiplegias showed increased temperature and the flaccid hemiplegias a decreased temperature. If this were so it might be that the thermal change was a purely secondary effect upon the disturbance in muscular innervation. However, it was later pointed out that Périssou's theory would not hold, because sometimes in a hemiplegia the upper extremity was warmer than normal and the

lower extremity cooler even though they were both spastic to the same degree

Recently Foerster and Kennard (39) have studied 32 patients, the majority of whom had old war wounds of the cortex. In 12 of 14 patients with long standing lesions of the excitable cortex (areas 4 and posterior part of 6) there was a constantly lowered temperature on the paretic side of the body. In two recently hemiplegic patients the temperature was increased. Nine patients with various other cortical lesions showed no detectible vasomotor disturbance.

Experimental analysis of the problem had until recently been very meager, apart from the early study of Eulenburg and Landois (33) who found an elevated temperature in the extremities of dogs after cortical lesions. Two years ago Pinkston, Bard and Rioch (102) made a detailed and highly important study in dogs on the influence of cortical lesions upon heat regulation. They found that removal of the cortex on both sides caused chronic vasodilatation, disturbed panting reflexes (slow and less responsive to rises in body temperature) and excessive shivering in response to cold. They found furthermore that removal of the frontal lobe was sufficient to bring on this state of vasodilatation of the extremities (102, p. 524). Pinkston, Bard and Rioch concluded that the highly integrated mechanism of heat regulation in the dog depended upon the integrity of the cerebral cortex. It should be noticed that in the realm of heat regulation autonomic and somatic integration occur concomitantly, *e g*, vasomotor changes and shivering.

Somewhat before Pinkston, Bard and Rioch's work was undertaken, Kennard (73, 75) had observed the vasomotor effects of cortical lesions in monkeys. She noted in 1932 after lesions of the premotor area, chimpanzees exhibited a fall of skin temperature in the paretic extremity (73). Kennard studied the phenomenon in some detail finding that the animal failed to show reflex vasodilatation when placed in a warm atmosphere. She found that the effect was specific to area 6 and could not be obtained from destruction of any other part of the cerebral cortex except that occasionally lesions of area 4 produced a slight, and usually transient, disturbance (75). The dog thus behaves differently from the monkey following a cortical lesion. From observations on stimulation it is evident that the cortex exercises some



regulatory control both upon the vasodilator and upon the vasoconstrictor mechanism, and Pinkston, Bard and Rioch point out (102, p 523) that in the dog the vasoconstrictor control appears to be dominant

It might still be urged that these vasomotor changes are secondary to motor paresis. That this is improbable is indicated by the different effect in dog and monkey (even though the somatic effects are similar), and the fact that in man the thermal changes are opposite to what one would predict on the basis of the somatic change *i e*, immediately following a hemiplegia in humans when the extremities are still flaccid, the skin temperature is increased, and when the extremities become spastic, the skin temperature tends to diminish and ultimately to become less than before. Furthermore in the monkey following an area 6 lesion, the vasomotor disturbance can be demonstrated long after the somatic paresis has passed off (75).

Aring (4) in a recent analysis of abnormal *shivering* in monkeys and chimpanzees has found that lesions of area 4 and of no other part of the cortex cause excessive shivering responses on slight lowering of the environmental temperature

André-Thomas (2) and Brickner (12) have pointed out that in hemiplegics there is generally a markedly exaggerated *pilomotor* reflex on the paretic side. This is best brought out by scratching the skin of the neck or pressing on the upper margin of the trapezius muscle. I know of no experimental studies on this point, but Dr Earl Walker has recently observed a similar phenomenon in a decorticate baboon. Unfortunately we do not know the cortical areas involved

Sudomotor and gastrointestinal changes are common after cortical lesions and they have been recently discussed by several authors (75, 135, 136) including Watts (134), but it is beyond the scope of this lecture to discuss them in detail. Watts and Fulton obtained marked increase in peristalsis of the small intestines on stimulation of area 6. Sheehan observed the stomach of fed monkeys could be inhibited from the same region (116).

## 2 *The cerebellum*

When communicating a paper this summer at the International Physiological Congress in Leningrad on the significance of overlapping

autonomic and somatic representation in the premotor area, it was mentioned that the premotor region of the cerebral cortex appeared to be the only part of the nervous system in which the autonomic and somatic systems had a focus of common integration. Almost the next paper on the program by Voronine and Zimkine (139), pupils of Orbeli, had to do with autonomic responses from cerebellar stimulation. They had found, following decerebellation, that animals generally exhibited prolonged constipation—an observation which I can confirm—but I had attached no significance to it until hearing Voronine and Zimkine's paper. They also found, in well-controlled and technically faultless experiments, that stimulation of the cerebellum caused marked inhibition of peristaltic movements of stomach and intestines, an effect similar to that which Sheehan (116) obtained on premotor stimulation. In view of the intimate structural and phylogenetic relations existing between these two parts of the brain, the result is not surprising, indeed there is some reason to believe that any form of representation existing in the motor regions of the cerebral cortex probably also exists in the cerebellum, and I would not be surprised if further investigation would lead us to a conception of ataxia and asynergia in autonomic regulation similar to that now held for cerebellar disturbances in the somatic sphere.

### 3 Discussion

Vasomotor disturbances of cortical origin have thus been demonstrated both in ablation and by stimulation. Gastrointestinal representation has also been demonstrated in cerebellum and cortex by both methods, and pilomotor and sudomotor disturbances have been seen following cortical ablation. In attempting to interpret these disclosures, attention is attracted first of all by the rather striking fact that somatic representation and autonomic representation overlap anatomically, most notably in the premotor region and apparently also in the cerebellum. From the same point which yields a rise of blood pressure complicated patterns of somatic response are readily obtained. Not only is there overlapping in the somatic and autonomic spheres, but there is likewise overlapping in the sympathetic and parasympathetic components of the autonomic representation. Thus in points intermediate between those which give rises and falls of blood

pressure, algebraical effects are frequently obtained as indicated by a slight dip followed by a slight rise in pressure. Sympathetic and parasympathetic representation have been separated and independent studies carried out through atropinization and peripheral nerve section (61).

Little can be said as yet concerning the pathways of autonomic outflow in the cortex. The recent important studies of Ranson, Kabat and Magoun (106) and of Kabat, Magoun and Ranson (71) on electrical stimulation of points in the forebrain and midbrain suggest that a cortical pathway descends through the internal capsule to the septum and then to the hypothalamic areas, and it is undoubtedly significant that anatomical connections between the cortex and hypothalamus have been described by Woollard and his co-workers and by Mettler (92) and others as passing through the septum, some passing through the septal nuclei and some directly to the zona incerta.

The significance of this overlapping representation lies in the fact that it makes possible simultaneous integrations in the autonomic and somatic spheres. To take a single example, Pinkston, Bard and Rioch (102) indicate that heat regulation which involves somatic, sympathetic and parasympathetic mechanisms is dependent for its final adjustment upon the cerebral cortex. Reflex dilatation in the dog and reflex vasoconstriction in the monkey become paralyzed following lesions of the excitable cortex, excessive shivering also results when the motor cortex is disturbed, and panting, the mechanism of heat loss in the dog, is also impaired. Here then we have a highly organized regulatory mechanism involving all parts of the motor outflow of the central nervous system, all integrated at the cortical level. May it not also be that somatic movements are accompanied by appropriate autonomic adjustments emanating from the frontal lobes, blood flow in the muscle, or changes of heart rate at the onset of movement?

## VI SUMMARY

Neurologists have frequently suggested that intention tremor, the outstanding symptom of cerebellar deficit in man, is caused by imperfect compensatory activities of the cerebral hemispheres. Experiments indicate (1) that in cat, dog and monkey tremor comes on after

decerebellation, only with the return of volitional movements, and (2) that after removal of both hemispheres from a decerebellate cat tremor is entirely absent from all reflex movements

In primates the motor regions of the cortex which may be involved in this imperfect compensation fall into two groups (designated in accordance with Brodmann's cytoarchitectural schema) the pyramidal region (area 4) and the extrapyramidal regions (areas 6, 8, 1-2-3, 5, 7 and 22) All these areas may play a part in the cerebral cerebellar interrelationship, but only those of the frontal lobe, *i.e.*, areas 4, 6, and 9-10-11-12 have thus far received detailed study (monkeys)

In a decerebellate monkey, a cortical lesion of *area 4* transiently *diminishes*, but never entirely abolishes, cerebellar tremor, removal of areas 4 and 6, however, is equivalent in its effect upon tremor to ablation of an entire hemisphere, the tremor being abolished for two to three weeks, slight tremor may ultimately reappear, evidently from ipsilateral innervation, since bilateral removal of areas 4 and 6 abolishes it permanently

Isolated removal of *area 6* of a decerebellate monkey, on the other hand, is followed by *augmentation* of cerebellar tremor Thus the premotor region evidently plays an important part in compensating for cerebellar deficit

The cerebral cortex also regulates certain autonomic functions In *dog* ablation of the hemispheres on both sides leads to (1) excessive shivering in response to cold, (2) an abnormally high threshold for panting, and (3) chronic vasodilatation of the skin, *i.e.*, the skin vessels are unresponsive to cold (102) In monkey and chimpanzee, area 6 is more intimately concerned with similar autonomic functions than area 4, as is evident both from ablation and stimulation

In *monkey* hemidecortication, or removal of area 6 alone, leads to gastrointestinal irregularities, paralysis of reflex vasodilatation and other disturbances which would affect heat regulation

In well-controlled experiments Orbeli and his pupils have recently observed disturbances of autonomic function on stimulation and ablation of the cerebellum

The coexistence in the same anatomical area of the cortex, as well as in the cerebellum, of autonomic and of somatic representation makes possible simultaneous and appropriate adjustments such, for example

as are necessary for heat regulation and somatic movement. Undoubtedly this overlapping also facilitates other cortically integrated reactions affecting both spheres of nervous outflow. The demonstration of automatic representation in the cortex thus becomes a disclosure of wide biological significance, and it bears eloquent testimony to the exquisite unity of adjustment in the living organism.

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## APPENDIX

The following protocols contain brief summaries of all operations (56) performed on 25 chimpanzees between October, 1930 and February 15th, 1936 Every chimpanzee used during this period is included except for ten unoperated specimens which are now under training in the Laboratory Unless otherwise stated operations were carried out under sodium amytal anaesthesia

The character of the disturbances in reflexes, posture, and autonomic function following each procedure is stated, special attention being given to the occurrence of spasticity or flaccidity In the headings to the protocols the sex, estimated age and actual weight *at the time of first operation* are indicated All specimens were sexually immature unless otherwise stated Indication is also given of those animals which have previously been described from the Laboratory Autopsy reports are given for the first time on the chimpanzees "Yama" (V) and "Mussai" (XI) which survived 5 years and 4 years respectively, and have been the subject of several reports from the Laboratory More detailed reports will be published in due course in the cases of Nos VII, VIII, IX, XIV, XV, XVI, XIX, XX and XXV which are described here for the first time

The experiments are divided into five groups in accordance with the site of the primary operation *i e*, (1) Area 4, (2) Area 6, (3) Areas 9, 10, 11 and 12, (4) Areas 1-2-3, and (5) other areas

## ABLATIONS OF AREA 4 (LEG)

I JOE *Male, 5 yrs old, wt 13 kg, rec'd Oct 14, 1930.*

*Left area 4a (Dec 3, 1930)*—This, the first chimpanzee of our series, had its leg representation (area 4a) removed from the left hemisphere under Dial anaesthesia. The animal sustained an enduring monoplegia of the right lower extremity, flaccid in character, 24 hours after operation the animal showed an unmistakable Babinski response which increased in intensity and ease of elicitation during the first week after the operation. This was the first time a Babinski response had been produced experimentally in an infrahuman primate. Motor power at hip began to return on the 8th day and thereafter recovery proceeded distally but no voluntary power was observable in the digits up to the 47th day when the next operation was performed.

*Right area 4a (Jan 21, 1931)*—After removal of area 4a from the right hemisphere there followed a similar flaccid monoplegia in the left leg with an enduring Babinski response accompanied by exaggeration of the Babinski in the right leg. Both lesions encroached somewhat on area 6 which undoubtedly accounts for the lateral deviation of the toes and the fanning sign of Babinski which this animal showed after the second operation. The animal continued under observation until Aug 6th, 1931, during which time the Babinski response remained positive on both sides, spasticity failed to develop, and little voluntary prehension of the toes was regained. The left cervical sympathetic was cut on Feb 13th, 1931, and the animal was lost on the operating table Aug 6th, 1931, when an attempt was being made to remove the right cerebellar hemisphere. A full report of this experiment has already been published (46, Experiment 14).

II SIS *Female, 4 yrs old, wt 13 kg, rec'd Oct 14, 1930*

*Left area 4a (Dec 31, 1930)*—Area 4a was removed from the left hemisphere under Dial anaesthesia, a Babinski response appeared within 24 hours, as in the preceding experiment, together with a conspicuous flaccid monoplegia of the right limb. Volitional movements of the hip appeared on the 6th day and thereafter power continued to improve, but no definite movement of the toes was observed for several months, the flaccidity diminished with return of power, no abnormal increase in resistance to passive manipulation was at any time observed.

*Right area 4a (Jan 8, 1932)*—The left area of the right hemisphere was removed 13 months after the left, this was followed by the appearance of a Babinski response in the left leg, augmentation of the Babinski on the right, and pronounced flaccid monoplegia, as in Experiment I.

*Transection of spinal cord (Jan 27, 1932)*—The spinal cord was severed at the eleventh thoracic level and detailed observations made on the differences of spinal shock on the two sides. A full report of this experiment has already been published (46, Experiment 15).

## III KINDIA Female, 4 yrs old, wt 14 kg, rec'd May 6, 1931

*Left area 4a for hallux (July 9, 1931)*—After identifying the hallux representation in the left hemisphere, this region was removed to see whether such restricted lesion would cause a Babinski response. The knee and ankle jerks were depressed on the right side immediately after the operation, but 3 hours later the animal died suddenly from a pulmonary embolism. The cerebral hemisphere was found to be in good condition immediately after death.

## IV PAU Mature female, 8 yrs old, wt 36.5 kg, rec'd May 6, 1931

*Area 4a (Dec 14, 1931)*—This animal, acquired from Dr Yerkes because it was unsuitable for training, began to lose weight soon after it was purchased, when it was realized that the animal was sick, its cortex was explored, with the usual aseptic precautions. The left foot area was removed and there followed the usual flaccid monoplegia with complete areflexia which continued despite active movements of the left leg until the animal's death from tuberculous broncho pneumonia some 30 hours after the procedure.

## V YAMA Male, 4 yrs old, wt 12 kg, rec'd Oct 14, 1930

This animal, which had been several times reported (46, Experiment 16, 47, Experiment 7, 77, Experiment 1, 114, Experiment 5), will be briefly summarized here. A diagram of its operations is included above in figure 12.

*Left area 4a (Jan 21, 1932)*—Removal of the leg area from the left hemisphere was followed by an enduring flaccid monoplegia of the right leg with a positive Babinski response and gradual return of voluntary power beginning at the hip on the 8th day. The toes had failed to show return of power on the 43rd day when the second operation was performed.

*Right area 4a (Mar 4, 1932)*—Removal of the right leg area was followed by left monoplegia, great depression of reflexes, impairment of previously regained voluntary power in right limbs and alteration in the reflex status in this extremity. Neither limb exhibited spasticity at any time prior to the third operation.

*Left area 6a (superior half, Dec 16, 1932)*—The superior part of the premotor area was removed and immediately thereafter the animal developed a spastic right lower extremity with great increase in deep reflexes, the appearance of the fanning sign of the Babinski, positive Rossolimo, Mendel Bechterew responses and grave additional impairment of voluntary power. The spasticity and the positive Rossolimo response persisted until May, 1935, when the animal began to look sick, and to our surprise the spasticity of the right lower extremity, together with the reflex signs increased in intensity, motor power at the same time diminished. As the animal seemed incurably ill, it was sacrificed on July 12th, 1935, and in addition to a generalized miliary tuberculosis and active tuberculosis in the lungs, the animal had an acute patch of tubercular osteomyelitis affecting the left bone flap and extending into the remaining lower part of the left premotor

area, clearly accounting for its increased symptoms before death. There were no excitable foci for the hind limbs in either hemisphere.

VI MIKE. *Male, 4 yrs old, wt 14.6 kg, rec'd Oct 16, 1931.*

*Left area 4a (Mar 29, 1932)*—Area 4a was removed from the left hemisphere of this animal in order to study the cortico-spinal degenerations after three weeks. The animal had a large tuberculous gland blocking the hilus of one lung and was blue and decompensated for several days after operation. During this interval the reflexes were brisk, i.e., the Babinski and Chaddock's responses were present immediately after the operation, tendon reflexes were not depressed and there was some volitional movement at hip within two days, but the limb was flaccid. The animal became compensated after two days and the right hind limb then began to show all the usual signs of 'cortical shock'—the Babinski response and knee-jerks were depressed on the right side, and from then on the monoplegic extremity emerged slowly from its reflex depression following a course similar to the preceding. It did not become spastic during the 15 days of observation. It was sacrificed for Marchi studies on April 13, 1932 (see 49, Experiment 1).

VII. SONG. *Mature male, 7 yrs old, wt 35 kg, rec'd June 5, 1933*

The subject of this experiment was a recently matured male chimpanzee which had been in Dr. Yerkes Laboratory for three years, it was well-developed and powerfully built. The experiment was planned to see whether area 4 lesions *per se* produced atrophy of the musculature.

*Left area 4a (June 5, 1933)*—After identifying the margins of area 4a by faradic stimulation, the entire region was removed in one block. The animal showed a profound monoplegia with marked depression of reflexes for three days and apart from slight flexor posture which returned at hip and knee, the extremity exhibited conspicuous flaccidity for the next four months, the extensors at knee and ankle remained completely without postural resistance and the toes at no time passed into a state of spasticity. The Babinski response was present after the second day. After about six weeks atrophy of the musculature became apparent and by the time of the second operation the atrophy was conspicuous. After four months there was no voluntary prehension of the toes but the animal could bring its foot to its mouth slowly and awkwardly.

*Spinal transection (Sept 26, 1933)*—The animal developed a severe diarrhea during late August and as its health seemed precarious, its spinal cord was cut at the mid-dorsal level with a view to studying the difference in extent of spinal shock on the two sides. The animal died 40 hours later.

*Autopsy* circumscribed lesion was found in the precentral convolution and histological examination revealed several isolated Betz cells just at the anterior wall of the lesion. The premotor area was normal. This experiment is to be reported in full at a later date in a discussion of cortical atrophies.

VIII DARBY *Male, 6 yrs old, wt 19.0 kg, rec'd June 14, 1934*

*Right area 4a (Apr 25, 1935)*—The leg representation in the right hemisphere was removed in a circumscribed block without damage to the postcentral convolution but with encroachment for a few millimeters into area 6. The recovery was characteristic, an essentially flaccid monoplegia with slight flexor posture at hip and knee when volitional power revived. The Babinski response was positive in the affected limb.

*Hypophysectomy (May 4, 1935)*—A complete hypophysectomy was carried out by Dr. William Mahoney, the first time such a procedure has been reported in a chimpanzee (*Amer J Physiol*, 1936, 116, 106-107). The animal had a persistently low blood sugar which was easily controlled by giving glucose. The animal died on May 21, 1935, from inhaling its vomitus while under anaesthesia. Throughout the month of its survival, no spasticity developed in the left hind leg. The muscles of the left lower extremity showed moderate atrophy. No Betz cells were found at the anterior edge of the lesion in sample sections. The block removed at operation which had been cut serially showed the anterior margin of the Betz cells in all sections.

IX LIBIA *Female, 2.5 yrs old, wt 7.5 kg, rec'd Sept 17, 1935*

*Left area 4abc (Oct 4, 1935)*—A thin strip comprising the entire extent of area 4 from cingulate gyrus down to the lower end of the face representation was removed in a single block with a view to illustrating the syndrome of a complete area 4 lesion in the chimpanzee—an ablation not previously attempted in this series. On the second day after operation the right extremities, which had at first shown conspicuous flaccidity, began to exhibit increased resistance in flexors and extensors, especially in the knee extensors of the lower extremity. Spastic resistance continued to increase and on the 4th day the hemisphere was reexplored, no clot was found and the premotor region was well vascularized. Thereafter slow return of power occurred proceeding from the proximal joints distally, but the moderate spasticity continued. The animal developed meningitis suddenly fifteen days after operation from a skin infection that developed after the re-exploration. Sample sections removed from the brain at autopsy indicated that the premotor area had not been seriously encroached upon by the precentral lesion. This experiment suggests, as do those of Dr. Hines (58), that an isolated ablation of areas 4a or 4b gives results quite different from a strip lesion which completely separates area 4 from area 6.

X GHANDI *Male, 5 yrs old, wt 22.2 kg, rec'd Dec 19, 1934*

*Left area 4a (Nov 8, 1935)*—The leg area was removed from the left hemisphere, after which the animal sustained a profound paresis of the right leg, flaccid in character which persisted until January 13, 1936, when the premotor representation was removed. Several days after the area 4 ablation power began to return at hip, later at knee and some flexor posture developed at three joints, and prior to



January 13, 1936, there was no gross resistance to passive manipulation and the extremity hung pendant as in the photograph (Fig 10, above) On Dec 4, 1935, the first and second temporal convolutions were removed from the right hemisphere, there were no postural disturbances as a result of this procedure, but a Jacksonian seizure occurred on the 3rd day affecting left face and head

*Left area 6a (Jan 13, 1936)*—The superior part of area 6 was removed from the left hemisphere, within 24 hours marked increase in resistance of the hip and knee flexors developed and increased in the ensuing days with transient forced grasping Motor power and its range of movements was greatly curtailed as a result of the premotor lesion This continued until its sacrifice

*Subsequent course*—On Feb 13, 1936, a small incision was made in its left occipital lobe, on Mar 31, 1936, its right superior cerebellar peduncle was cut and on Apr 3 it was sacrificed by Dr A. Earl Walker who will report the experiment in detail in his study of the thalamocortical projections in chimpanzee

#### ABLATIONS OF AREA 4 (ARM)

XI MUSSAI *Male, 6 yrs old, wt 23 0 kg, rec'd Oct. 16, 1931.*

The present experiment has been several times reported (47, Experiment 8, 17, Experiment 4, 77, Experiment 4, 68, Experiment 2), but its autopsy is now recorded for the first time The animal had seven lesions as follows: Left area 4b (arm, Apr 29, 1932), right area 4b (May 13, 1932), left area 6a (Nov 11, 1932), right area 6a (Jan 13, 1933), right frontal areas (Nov 3, 1933), left frontal areas (Dec 15, 1933), and finally section of right cerebellar peduncles (Nov 6, 1935) which was followed by operative fatality. In each of the two primary operations, involving ablation of the left arm areas, the posterior part of area 6 was extensively encroached upon, in both instances the animal developed a transiently flaccid monoplegia of the arm, which was followed after three to four days by the assumption of hemiplegic posture accompanied by moderate spasticity at elbow and wrist In both instances however the spasticity passed off within another two to three weeks when the animal began to resume using the extremities for volitional movements The animal never regained active prehension of the digits After removal of the premotor regions, first on one side and then from the other, strong and enduring (two years) spasticity developed in both upper extremities, the spastic condition affecting flexors and extensors alike, and being particularly prominent in the digits After these two operations the animal was not able to feed itself again with its hands for nearly two years after which time the right hand was occasionally clumsily brought to the mouth bearing food The removal of the frontal association areas slightly increased the spastic disability, probably owing to removal of a small strip of premotor tissue in the posterior part of the frontal block

*Autopsy* showed virtually all the frontal lobe had been removed except for areas 4a on both sides, and a part of the orbital surface on the right side The caudate nuclei had not been encroached upon The whole brain has been cut in

serial sections and will be reported by Dr A. Earl Walker in his studies of the thalamocortical projections

ABLATION OF AREA 6A

XII BOY *Male, 3 yrs old, wt 13.5 kg, rec'd Sept 5, 1932*

The subject of this experiment had been trained in problem box manipulation by Dr. Jacobsen. He was a healthy, vigorous, male specimen, cooperative and easily handled.

*Left area 6a (Sept 9, 1932)*—Following removal of a large block of area 6 tissue from the left hemisphere forced grasping immediately appeared in both right extremities which persisted for about ten days when it gradually disappeared with the resumption of active volitional movements. The deep reflexes were increased on this side for about two weeks. There were vigorous tendon responses of the digits (signs of Rossolimo and Hoffman). There was also a grave and enduring disturbance of skilled movements and transient vasomotor disturbance.

*Right area 6a (Jan 9, 1933)*—A corresponding block of premotor tissue from the right hemisphere was removed a month later which caused the symptoms previously present on the right side to reappear, i.e. spasticity, forced grasping and increase of tendon reflexes and similar symptoms, somewhat more grave than after the first operation appeared on the left side. The spasticity affected all muscle groups, but was most pronounced in the flexors of the upper limbs and the extensors of the lower. Spasticity diminished after two to three weeks on the left, but persisted for over a month on the right. The animal was kept under observation until May 29, 1934, at which time the extremities had been normal to passive manipulation but tendon reflexes of the digits, especially the toes continued moderately increased. Dr. Jacobsen's training technique continued to disclose disturbance of skilled movements. Preliminary reports of the experiment have already been published (47, Experiment 3, 77, Experiment 2, 68, Experiment 3).

XIII SAMBO *Male, 6 yrs old, wt 28.0 kg, rec'd May 10, 1932*

The animal was a vigorous adolescent male, with remarkable muscular development.

*Left area 6a (Jan 30, 1933)*—Following removal of the left premotor area, somewhat more deeply and radically than in No. XII, the animal exhibited a more profound and enduring paresis than the preceding, and it showed a positive Babinski response which persisted for 8 days. The upper extremities assumed a spastic hemiplegic posture which increased in intensity during the first week and the lower extremity became markedly spastic after the 6th day. Forced grasping was present, increasing in intensity as the spasticity increased. All muscle groups were affected, but the extensors showed somewhat greater resistance than the flexors, both in the upper and lower extremities. Spasticity reached its height

about the 8th day and then gradually diminished with return of voluntary power. Forced grasping continued, however, for over a month and increased tendon reflexes were still present three months after operation.

*Right area 6a (Apr 24, 1933)*—After the right premotor area was removed there was a conspicuous return of symptoms on the ipsilateral side with the usual premotor syndrome on the opposite side i.e., forced grasping, generalized increase of resistance to passive manipulation ('cog-wheel' in type) impairment of skilled movements and vasomotor disturbance. On June 2, the left extremities were still moderately spastic especially the lower extremities, and when the animal was emotionally excited, strong forced grasping developed. The animal had meanwhile become dangerously unmanageable and a third operation was performed to incapacitate it.

*Left area 4a and b (June 2, 1933)*—The motor representation of the leg and arm was removed after the left hemisphere after which all reflexes became depressed, but the depression lasted less long than in animals in which area 4 had been removed as a primary procedure. Ultimately very strong spasticity developed on the right side affecting all muscle groups, and the motor disability and posture closely resembled that of a long-standing hemiplegia in man. The hands were maintained in a claw-like posture, with hyperextension at wrist and at the metacarpophalangeal joints. There was lead-pipe rigidity of biceps. In Nov. 1933 the animal developed an obscure diarrhea and was sacrificed.

*Autopsy*—The brain showed lesions described above, the area 6 lesion being complete and they had encroached slightly upon the frontal association areas. The right pyramid was completely degenerated. A preliminary report of this experiment has been published (17, Experiment 5, 77, Experiment 3).

#### XIV EDITH *Female, 3 yrs old, wt 12.0 kg, rec'd June 14, 1933.*

The subject of this experiment was a tame and easily handled young female.

*Left area 6a (Oct 18, 1933)*—Extirpation of the premotor region was followed by complete area 4 and 6 syndrome due possibly to disturbance of the circulation in area 4, i.e. this was initial depression of reflex, a positive Babinski's sign, etc. These signs gradually became less conspicuous, however, leaving moderate forced grasping and moderate spasticity which persisted for about a month and then disappeared. The animal also had a marked vasomotor syndrome of the left extremity with paralysis of reflex vasodilatation studied by Dr Kennard. The animal was kept under observation without further surgical procedure until Feb 6, 1935, when it was hypophysectomized, and died from a gastric perforation (preceded by hemorrhage), 24 hours after the hypophysectomy. The animal's premotor syndrome was complicated by the development of marked muscular atrophy of the right extremity, especially the right leg. Throughout most of its postoperative course the Babinski response has been occasionally positive, we have therefore been inclined to attribute the atrophy to concomitant injury of area 4. Microscopical examination of the block removed at operation showed no damage to Betz cells.

XV ANNA *Female, 6 yrs old, wt 25.4 kg, rec'd June 11, 1933*

*Left area 6a (Feb 23, 1934)*—Left premotor region was removed from this animal with a view to studying the subcortical degeneration by Marchi technique after three weeks. Though the animal was uncoöperative and difficult to examine it was obvious that it had developed the usual premotor syndrome with spasticity, forced grasping, vasomotor disturbance and impairment of skilled movements. Extensive compensation had begun to show itself before the end of the third week. The animal was sacrificed March 13, 1934, and Marchi studies were made by Dr. Stephen Poljak of Chicago who will ultimately report his findings.

XVI BLANCHE *Adult female, 14 yrs old, wt 33 kg, rec'd Mar 11, 1933*

The present animal, a mature female, was sent from another laboratory for sacrifice because of a skin disease resembling pellagra. On Mar 11, 1933, areas 4a and b and 6a were removed from the left hemisphere and the animal was sacrificed 52 hours later for study of the degeneration of *boutons terminaux* in subcortical centers and in the spinal cord. The right arm became spastic after 48 hours, but the right leg was still flaccid at the end of 52. No vasomotor changes were observed. This experiment will be reported by Dr. E. C. Hoff in his studies of bouton degeneration in the chimpanzee.

## ABLATIONS OF AREA 9-12

XVII LUCY *Mature female, 9 yrs old, wt 26 kg, rec'd June 14, 1933*

This animal and No. XVIII, though still living are included in the protocols since autopsy material will probably not be available for several years more. After 9 months of training by Dr. Carlyle Jacobsen, the left frontal association areas were removed on Mar 16, 1934, in a block weighing 14.5 grams. The animal made a prompt recovery, and after the first 24 hours there was no evidence of motor disturbance or postural weakness. On May 25, 1934, the frontal association areas were removed from the right hemisphere in a block weighing 21.5 grams, more of the orbital surface of the frontal lobe being taken in this operation. Again the animal recovered with a very slight degree of spasticity in elbow and left shoulder which passed off after 3 days. The observations are important from the point of view of cerebral-cerebellar relationships since they indicate that bilateral removal of areas 9, 10, 11 and 12 (the frontal association areas) does not cause significant motor or postural disturbances.

XVIII BECKY *Female, 5 yrs old, wt 16.2 kg, rec'd June 14, 1933*

This, the second of Dr. Jacobsen's animals trained for study of the frontal association areas, is also still alive. On Mar 22, 1934, the frontal association areas were removed in a block weighing 18 grams. The animal made a smooth recovery from the operation and at no time did it exhibit motor weakness or postural disturbance, apart from a slight reluctance to use its right arm for several

days after the procedure On July 12, 1934, the right frontal association area was removed in a block weighing approximately 15 grams Again the animal recovered without significant motor disturbance and it has continued alive for a period of more than 2 years with normal motor coordination These observations have been reported in preliminary form by Jacobsen, Wolfe, and Jackson (70)

#### POSTCENTRAL ABLATIONS

##### XIX CARRIE NATION *Female, 4 yrs old, wt 9.9 kg, rec'd Sept 19, 1935*

This and No XX were chimpanzees used by Dr A Earl Walker for study of the thalamocortical projections On Sept 25, 1935, the entire postcentral convolution including areas 3-1-2, as well as areas 5 and 7 of the parietal lobes, were removed in a single block weighing 11.3 grams The tip of the prefrontal cortex was removed at the same operation The animal was extremely difficult to examine, being aggressive and uncooperative but from inspection of its movements it was clear that the right extremities exhibited little if any motor paresis, but there were obvious signs of sensory disturbance In feeding she preferred to use her left hand but when provoked, or when attempting to escape, the extremities on the right and left side were used with almost equal force Those on the right were awkward and sometimes assumed unnatural positions, but there was no tremor or ataxia The animal continued without much change until Dec 10th Autopsy showed that the frontal lobe had not been involved by the lesion

##### XX TOMMIE *Male, 6 yrs old, wt 20.5 kg, rec'd Dec 19, 1934.*

The present animal has been trained in sensory discrimination by Dr Ruch prior to its postcentral lesion The opposite extremities were then incapacitated by a lesion of the precentral convolution in order to force the animal to use the extremities having sensory deficit

*Areas 3-1-2 (Nov 4, 1935)*—Following complete ablation of the postcentral convolution, *i e*, areas 3-1-2, the animal exhibited a transient hemiplegia and developed extensor spasticity of its upper extremity with slight flexor spasticity There were no pyramidal tract signs

*Left areas 4ab and 6a (Dec 6, 1935)*—After removal of the motor and premotor areas from the left hemisphere the right extremities exhibited complete flaccidity for two days, and thereafter gradually increasing spasticity developed affecting all muscle groups in the upper and lower extremities The spasticity reached its height at the end of about a month, the hand assuming a claw-like posture with hyper-extension at the wrist and metacarpophalangeal joints, the spastic state continued with very little amelioration until the animal was sacrificed May 14, 1936 The animal regained sufficient power of its right hip to use the spastic limb for walking, but practically no other purposeful movements were regained in arm or leg, indeed, the animal was quite unable to feed itself with its right hand at the time of sacrifice

*Right areas 5 and 7 (Feb 7, 1936)*—The remainder of the parietal lobe was

removed from the right hemisphere, and while this somewhat increased the somatic sensory disturbance there was no change in posture. This experiment will be reported in full by Dr. Ruch from the point of view of sensory discrimination and by Dr. A. Earl Walker in his studies of the thalamocortical projections.

## MISCELLANEOUS LESIONS

XXI PEG *Female, 4 yrs old, wt 15 kg, rec'd Feb 4, 1935*

The present chimpanzee was a young female used for study of the effect of section of the 3rd nerve. It died prematurely Mar 11, 1935, following operation.

XXII KANI *Mature female, 9 yrs old, wt 35 kg, rec'd May 24, 1933*

The observations carried out on the present animal are significant only as controls. The animal had been highly trained in problems of visual discrimination by Dr. Spence. On May 24, 1933, its left occipital lobe, including areas 17 and 18 was completely removed from the left hemisphere. Thereafter the animal exhibited complete and permanent right homonymous hemianopsia and slight right sided motor weakness which passed off within 2 days. On July 7, 1933, areas 18 and part of 17 were removed from the right hemisphere, and again the animal failed to exhibit any enduring motor or postural deficit. This animal has been reported by Spence and Fulton (118), and full anatomical studies of the brain by Poljak and Hayashi (*Brain*, 1935, 59, 51-60).

XXIII BONZO *Male, 4 yrs old, wt 16.5 kg, rec'd May 10, 1933*

The present animal was a nephritic (lead poisoning?) specimen whose spinal cord was transected in order to study the phenomena of spinal shock on Nov 24, 1933. It died within 24 hours after operation.

XXIV SELA *Female, 7 yrs old, wt 20 kg, rec'd May 6, 1931*

A tuberculous specimen obtained from Dr. Yerkes this animal proved difficult to handle and on Dec 7, 1931, was subjected to a lateral semisection of the spinal cord. The animal was ill at the time of operation, but it survived 3 days, during which time symptoms of profound spinal shock were present in the right lower extremity on the side of the semisection.

## HEMIDECORTICATION

XXV MARY *Female, 5 yrs old, wt 21 kg, rec'd June 13, 1935*

The left cerebral cortex of this chimpanzee was removed without injury to basal ganglia or thalamus on Sept 11, 1935 for Dr. Walker's study of the thalamocortical projections. The postural and motor status of the affected extremities in this animal was compared with No. XX after removal of areas 4ab and 6a. The postoperative course was strikingly similar in the two cases, for the first 48 hours the right extremities were completely flaccid and parietic with greatly de-

pressed tendon reflexes, on the third day the hemiplegic posture began to be assumed and generalized spasticity appeared, most prominently in the knee extensors and elbow flexors. The spasticity increased steadily for about a month in all muscle groups and then continued without much change until sacrifice Nov 15, 1935. During this interval associated movements were present, a little volitional flexion at hip and shoulder was regained, but the extremity was never used effectively in walking. At the time of sacrifice 10 weeks after operation this animal was less far along in motor recovery than No. XX at a corresponding period after ablation of areas 4ab and 6a. The experiment will be reported in detail by Dr. Earl Walker in his study of the thalamocortical projections, and by Walker and Fulton in a comparative study of the effects of decortication.

# ANAEMIA OF INFANCY AND EARLY CHILDHOOD

HUGH W JOSEPHS

*From the Harriet Lane Home of the Johns Hopkins Hospital and the Department of Pediatrics,  
Johns Hopkins University, School of Medicine, Baltimore, Maryland*

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## FOREWORD

In dealing with the literature I have tried to keep the purpose of the paper in mind. This purpose is to present the present status of our knowledge of anaemia in infancy and early childhood especially its etiology, pathogenesis, clinical characteristics, and therapy. Pathological pictures are not given in any detail and in general are included only for the light they may throw on the nature of the process by which the anaemia has developed. Experimental anaemia is not reviewed, although reference to experimental work will be included where it contributes to the discussion. We attempt in animals to isolate and study a single mechanism, the conditions of a single equilibrium, we have no proof that that same mechanism will be the one at work in the human. The mechanism of rachitic bone changes may be the same in rats and babies, rickets of rats is not the same as rickets of babies. In anaemia we are not even sure that the mechanism is the same.

No attempt is made in this work to apportion priority either of

observation or of conception. Few articles written before 1915 have any value except historically, so that only an occasional reference is made to them. I have looked for facts rather than for opinion unless the opinion is based on a wide personal experience or unless it is accompanied by sufficient evidence to allow the reader a basis for criticism. For the support of the statements made in this paper I have confined myself predominantly to the pediatric literature, using examples drawn from "adult" literature only to fill in the gaps. In an attempt to cover the literature of the last ten years, there will naturally be some oversight, but in general, omission is due either to the fact that the data on which statements are made have been omitted, or to the fact that the results as stated are insufficiently controlled.

### INTRODUCTION

Infancy is a period in which anaemia is particularly prevalent. The reasons for this lie partly in the constitutional or physiological peculiarities of the infant, partly in the external factors that disturb in various ways the equilibria on which the normal state of the blood depends. In this sense anaemia is not to be considered a disease, but is the result of a disturbance in normal physiological processes which may be brought about by disease or constitutional defect on the one hand and on the other by factors that are entirely extrinsic. The study of anaemia should be an attempt (1) to recognize these factors, extrinsic and intrinsic, (2) to understand in what way they disturb the normal physiological processes and finally (3) to learn how to eliminate them or modify their influence.

### A CONSTITUTION

As this term is used, it has three different meanings, or rather its various usages can be grouped under three heads.

1 It is used to denote tendencies common to all individuals at a given age. In so far as such tendencies are the common property of all they are to be considered physiological, but in some individuals they are more marked and last longer, and in this sense may be considered pathological. The newborn period is of particular importance

from this point of view, being one of adjustment in which new equilibria must be established and new processes developed

a Any lack of a well established equilibrium results in the lability of function that is one of the characteristics of infancy, marked in the newborn period, especially so in premature babies and others for any reason unready to assume the functions of extra-uterine life. Wide swings in haemoglobin, like wide swings in water balance or in temperature, may occur under provocation too slight to produce changes in older children or adults. This tendency grows less as the child grows older, but it may be prolonged under conditions that impede the proper development of the child.

b A second characteristic of infancy is the ease with which the rate of hemolysis is increased, and blood formation may revert to an earlier embryonic stage. White cell formation often takes part in this process, resulting in the so-called "pseudoleukaemic" pictures.

Other factors having a bearing on the incidence of anaemia and the peculiarities of the blood picture that might be mentioned are a tendency to *lymphocytosis* commonly seen in infancy under certain conditions, infrequency of "*aregenerative*" anaemia compared with later periods, *rapid gain in weight* resulting in intensification of any deficiency that may be present, relatively low incidence of severe infection in the first six months of life.

2 Another sense in which the term "constitution" is used is to explain why some individuals act differently from the average. This meaning is frequently encountered in the German literature, especially as "Konstitutionelle Minderwertigkeit." A conception as vague as this is not very useful and is likely to be applied too readily to anything not well understood. As knowledge increases, however, not only may we find that many things attributed to differences in individual make-up are actually the result of extrinsic factors at present little more than suspected, but also we shall be able to define this phase of "constitution" in terms of the processes involved.

3 By some the term "constitutional" is confined to those conditions (also called "congenital") in which there is definite evidence of something wrong with the make-up of the individual. This evidence consists in abnormalities of structure, of familial, hereditary, or

racial tendencies, or abnormalities of function that exist throughout a lifetime

The factors included under the term "constitutional" might just as well be called "intrinsic," "underlying," "predisposing." Those types of anaemia in which the constitutional factors completely dominate the picture are often designated "primary." In such cases anaemia exists as a result of some deep seated defect in the haemopoietic function, so that extrinsic factors have only a secondary influence. In the great majority of cases, on the other hand, the constitutional factors predispose to the development of anaemia, or to a particular type of reaction, while the extrinsic factors play the part of precipitating cause. Nor is this statement entirely true, there is rather a multiplicity of factors acting together to a common end. The desire for a simple classification for the teaching of students and for the purposes of filing cabinets has caused a division of the material into primary and secondary which is purely artificial and does not reflect the actual state of affairs.

#### B MECHANISM

Blood pictures are dependent on interrelations between processes, any disturbance of which necessitates the development of a new equilibrium. The point at which this new equilibrium is established is dependent on the severity and type of disturbance as well as the underlying ability of the tissue involved to respond to the necessity for readjustment. The processes involved in these interrelations are not many. They may be included under the following: (1) Synthesis of haemoglobin, disturbance of which may arise from deficiency in either material or process. (2) Regenerative ability of the haemopoietic tissue. Inability to form red cells rapidly enough to compensate for loss or destruction that is not excessive is designated by the term "hypoplasia" which must therefore be understood in a functional rather than anatomical sense. (3) The process of blood destruction. (4) The process of maturation, disturbance of which gives rise to the various forms of erythroblastosis and if the white cells are involved to "pseudoleukaemic" pictures. The study of the mechanism of anaemia is the study of the part played by each of these processes in the production of the final equilibrium, and the speed with which it is

attained Much of the confusion that exists is due to the mistake of regarding blood pictures as specific Blood pictures are the result of disturbances in processes in whatever way those disturbances are brought about, whether by infection, poisons, nutritional deficiencies, constitutional defect or disease of organs involved in the regulation of blood formation and destruction

## THE NORMAL BLOOD PICTURE OF INFANCY

### A THE NEWBORN PERIOD

#### *1 Red cells and haemoglobin*

The usual statement concerning the course of the red cells and haemoglobin as found in the text-books is about as follows The newborn baby comes into the world with a supply of haemoglobin and red cells far in excess of that which is considered normal for the needs of extra-uterine life, so that during the first six weeks there is a rapid fall from the values usual at birth This fall may be excessive, reaching levels from which recovery takes place to the values which will tend to be maintained during the remainder of the first year The statements in the text-books are, however, based for the most part on earlier work and fail to mention a number of facts that have come to light in the past ten years In this paper I have summarized only the more recent work, stressing particularly those observations which tend to modify the accepted conceptions (The figures for haemoglobin are summarized in chart 1 )

a Polycythaemia at birth, which has been so stressed in the text-books and all the earlier publications, is not a characteristic of all recent statistics (72, 180, 252, 415, 486, 487, 738) Merritt and Davidson's (457) is about the only recent publication that confirms its existence, and even in their work it is only moderate in degree, since counts above six and a half million were only rarely encountered In babies who are cyanosed for any reason, polycythaemia may be extreme, especially in congenital cardiac disease, and in these cases the red cells and haemoglobin often do not follow the usual course, but fall gradually

b Lower limit of normal Counts under four and a half million at birth are rare in all statistics This does not mean, however, that all counts below this level are to be considered pathological This point will be considered later in the section on anaemia of the newborn period

c Extent of fall in red cells and haemoglobin The red cells rarely fall to a point below three and a half million, reached at the end of

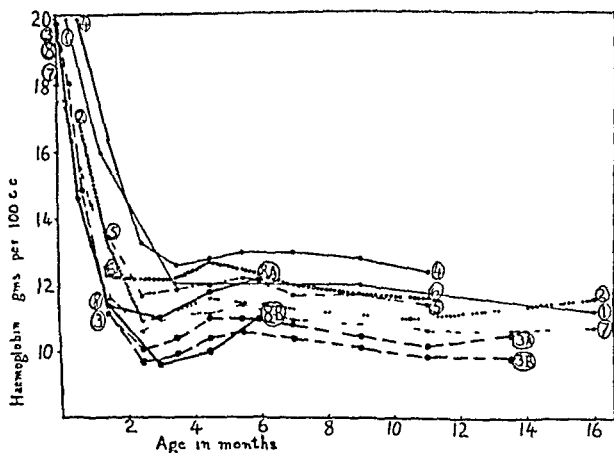


CHART 1 COMPOSITE HAEMOGLOBIN CURVES FROM DATA IN THE LITERATURE

1, Appleton, 2, Drucker, 3, McKay—A, breast fed, B, artificially fed, 4, Merritt and Davidson, 5, Elvehjem, Petersen and Mendenhall, 6, Usher, McDermot and Lozinski, 7, Kato and Emory, 8, Josephs (See text (Physiological Anaemia))

about two months, but values below this level are not to be considered necessarily pathological The variation in haemoglobin values of the different observers is considerable but the form of the curve is the same It is probable that the discrepancies are largely a matter of method Williamson's figures, which have long been considered standard, were obtained by a spectrophotometric method and give high values Merritt and Davidson's figures which are also high were obtained by calculating the haemoglobin from the iron content of



the whole blood It has, however, been shown that there may be a considerable amount of iron in the blood not combined with the haemoglobin especially in the first six weeks of life (319). In the other curves, the discrepancies are not so great until the seventh or eighth week when extrinsic factors begin to exert an influence on the haemoglobin

d Color index This is consistently high during the newborn period, tending gradually to fall until at about three months it reaches a value that will be maintained throughout infancy in normal cases

## 2 *Size of red cells*

Throughout the first week of life there is marked anisocytosis with tendency to macrocytosis (72, 131, 284, 576, 728) The average diameter lies in the neighborhood of  $8.5\mu$  or slightly above Cells with a diameter above  $10\mu$  are not infrequent, but none have been reported above  $12\mu$  in diameter These large cells usually form about one or two per cent of the total, tending to disappear at about the end of the first week, but sometimes persisting into the third week of life The average diameter after the first week gradually becomes less reaching "normal" (adult) values by the sixth month (534) Van Creveld (131) has noted a transitory increase in size at about the eighth week corresponding to the increase in reticulocyte percentage The changes in mean corpuscular volume correspond to those of the mean diameter just described—higher than "normal" (adult values) at birth ( $110\text{--}115\mu^3$ ) (251, 263, 474) gradually falling to the adult values at about the sixth month

## 3 *Reticulocytes and nucleated red cells (table 4)*

At birth, reticulocytes are present to the extent of about five or six per cent (208, 283, 328, 369, 457, 510, 624) They become reduced rapidly, and reach low values by the end of the first week, at times even virtually disappearing from the blood stream This state of affairs lasts for two or three weeks, then the numbers begin to rise slowly, reaching a peak of two to three per cent at about the end of the second, or during the third month (131, 202, 283, 317, 510) This corresponds to the time at which normally the red cells and haemoglobin are beginning to rise after reaching their lowest values and

also, according to Van Creveld (131) corresponds to a transitory increase in the mean diameter of the red cells. The reticulocytes gradually fall again as the haemoglobin and red cells attain the higher values characteristic of the end of the first half year of life. These changes take place with regularity but may vary in respect to the time of occurrence. They are therefore best studied in individual cases, and not by the statistical method which would tend to minimize the individual variations.

Normoblasts (12, 88, 415, 634) are frequently encountered on the first day of life, but rarely exceed 400 to 500 per cubic millimeter. They disappear rapidly and by the third day are rarely seen. Higher values than these are, however, occasionally seen in babies otherwise normal. (Lippman, (415) 37 per cent of white cells, Bungler and Schwartz (88) 22 and 24 per cent of white cells, Altitzoglou (12) up to about 2500 per cubic millimeter.) While in these cases the infants were apparently well, in other cases the prognosis has not been good. Erythroblasts more immature than the normoblasts are not present under normal conditions (88).

The minimum resistance to hypotonic salt solution has usually been found normal or slightly reduced in the first week of life. It has occasionally been found to begin as high as 0.6 (Bernheim-Karrer u. Grob (56), 0.48-0.54-5 per cent above 0.54, Hallez (266) average 0.56, maximum 0.64, Mitchell, (473), usually normal, maximum 0.55, Pollitzer (558), normal, Carr (98), average 0.45, maximum 0.5, Goldbloom and Gottlieb (230), as high as 0.8). The span of hemolysis tends to be increased (Hallez, Mitchell, Carr). There is no constant relationship between the minimum resistance and the presence of icterus (Mitchell).

#### *4 Constituents other than red cells and haemoglobin*

The constituents other than red cells and haemoglobin may be briefly considered.

a. The white cells (88, 199, 288, 601, 607) at birth average about 17,000 but such an average is almost meaningless when the counts vary normally between 30,000 and 6,000, and even in the same infant may vary over a wide range. The numbers gradually diminish during the first week or ten days. There is a shift toward immaturity

at birth so that myelocytes are frequently seen. This shift becomes less and disappears during the first week. During the first week the variations in numbers of white cells are conditioned by the myeloid elements, but as the total number falls the percentage of lymphocytes rises until at the end of the first week these form more than fifty per cent.

b The platelets (51, 170, 180, 415, 434, 457, 634) are somewhat lower in the first week than later, but these lower values are not apparently of much significance from the point of view of a tendency to haemorrhage since the values are rarely below 100,000.

c The clotting time is normally not prolonged, or at most not more than a minimal amount (98, 170, 457, 721).

d Bleeding time has been reported to be increased in normal infants without tendency to haemorrhage. Usually it is within normal limits (98, 457, 721).

#### B EFFECT OF PREMATURITY

In general the effect of prematurity is seen in an exaggeration of many of the characteristics we have already discussed. Starting from the same or higher point, the red cells and haemoglobin after about six or eight weeks reach a level somewhat below that in full term babies (7, 288, 318, 378, 407, 430, 441, 458). There is less tendency to the spontaneous rise which is seen in the normal baby at the end of the second month (7, 288, 318, 430, 441, 458). While these tendencies are not shared by all premature babies, it is clear that the lower the birth weight, the more likely are they to be present, and even full term twins and infants low in birth weight behave in like manner. The reticulocyte counts tend to be higher at birth, (441, 477, 624) and the rise occurring at about two months is greater corresponding to the lower level of the haemoglobin at this time (318). Nucleated red cells are more frequently encountered and persist somewhat longer but are rarely seen after the first week (288, 88, 440, 599, 607). While the white cell count is in general no higher, the shift toward immaturity is often more marked.

#### C INFANCY BEYOND THE NEWBORN PERIOD

The newborn period is, as already seen, characterized by rapidly falling red blood cell and haemoglobin values. These fall with great

rapidity until about the sixth week, then more slowly until about the tenth week when a gradual rise takes place, which continues to the sixth month. The spontaneous rise in haemoglobin was first pointed out by McKay and is present in all the curves of chart 1. From the sixth to the twelfth month, the haemoglobin tends to fall slightly again. During the second year it rises slowly and continues to rise until normal values are reached. The red cells after the first two months tend to rise more rapidly than the haemoglobin so that the color index tends to fall below unity, especially after the three months, and maintains a value of about 0.8 to 0.9 for the remainder of the first year. The discrepancies between the curves obtained by different authors depend probably partly on the methods and instruments used, but, beyond the newborn period, more largely on extrinsic factors such as social status, care in feeding, climate, time of year, exposure to infection, etc. The higher values obtained by Williamson (not included) and by Merritt and Davidson have already been ascribed, at least in part, to the methods used. Usher, McDermot, and Lozinski's values were obtained from infants in an asylum in which apparently the feeding and care of the babies is more carefully supervised than in most. Elvchem et al.'s values were from infants in a small, largely non-industrial town, Kato and Emery's from infants from a section of Chicago where the people are fairly well off, with negroes excluded from the statistics, McKay's (427) (1) from artificially fed infants in the poorest section of London and (2) from breast-fed infants in the same section.

The curves of chart 1 represent averages. The minimum values frequently fall in a range that by most would be considered anaemic. This tendency to anaemia used to be considered a normal occurrence in infancy and the term "physiological" was applied to it. The work of Helen McKay (428) in London has demonstrated the importance of an adequate supply of iron in preventing these low haemoglobin values, so that this "anaemia" can no longer be considered as physiological. She ascribes it to iron deficiency. As will be seen later, anaemia that is cured by administration of iron may occur under a variety of conditions, and the mere fact that haemoglobin rises after iron administration is not proof that iron deficiency was the essential cause.

## D PHYSIOLOGICAL ANAEMIA

I have called the newborn period one of adjustment and have included in it the first six weeks of life. The termination of the newborn period at six weeks is not as arbitrary as it might seem at first sight, but has been arrived at by a study of two sets of curves, those of McKay and those of Josephs (317). As already stated, McKay (A) represents artificially fed babies and McKay (B) breast-fed babies, other conditions being the same. Josephs (A) represents babies in The Florence Crittenton Home, where they were cared for by their mothers with no attempt at segregation, although they were not overcrowded. Josephs (B) represents babies cared for on the metabolism ward of the Harriet Lane Home, segregated from the regular wards and under the supervision of one nurse and one or, at most, two physicians. As a group, these latter babies have been remarkably free from infections and have developed much more as they would in a good private home. Both groups came from the same social background, received essentially the same type of feeding. The only difference seems to lie in the possibility of exposure to infection. Any severe infection in the first group excluded the baby from the series.

In both these sets of observations, the separation of the curves took place at about six weeks. Furthermore, in McKay's group of cases receiving iron from birth, the effect of iron in causing a higher level of haemoglobin began to be noticed at about six weeks (427). This behavior of the haemoglobin curves is interpreted to mean that up to six weeks of life the dominant factors influencing the red cells and haemoglobin are common to all babies and are therefore physiological or intrinsic while, from the sixth week on, the haemoglobin and red cells are increasingly under the influence of extrinsic factors, in one case exposure to infection, in the other nutritional [(1) breast feeding as opposed to artificial and (2) administration of iron]. If the term "physiological anaemia" is to be retained, it should properly apply only to that period in the second month of life when the haemoglobin has reached a low value that cannot yet be influenced by the correction of any responsible extrinsic factor. As may be seen from the curves, the application of the term "anaemia" to such a level of haemoglobin is open to question.

E MECHANISM OF CHANGES IN HAEMOGLOBIN AND RED BLOOD CELLS  
IN NEWBORN PERIOD

The newborn period is one in which the organism is required to adjust itself to a fundamental change in environment, and equilibria that were determined by the conditions of a parasitic existence must become readjusted now that the conditions are changed. We know very little of the factors regulating the formation and destruction of blood, and to what extent these processes in the fetus are influenced by factors derived from the mother. Probably not to any great extent, for anaemia in the mother is only exceptionally attended by anaemia in the newborn baby, and the makeup of the fetal blood is so different from that of the mother that one must assume a largely independent mechanism. The high red count and haemoglobin at birth have been attributed to the relatively low oxygen tension in which the fetus must exist, and the fall is considered analogous to the fall that occurs following descent from a high altitude. The presence of increased reticulocytes has been shown at high altitudes, but normoblasts and increase in white cells do not ordinarily occur, so that these evidences of bone marrow activity require some explanation other than anoxaemia alone. Weber's (Naegeli, p 582) observation that, at high altitudes, the reaction to poisons affecting the blood was more violent with normoblasts and other evidences of immaturity, may have some bearing on this question.

Shortly after birth there sets in an increased rate of blood destruction to which has been attributed the rapid reduction of red cells and haemoglobin. Attempts to determine the rate of destruction quantitatively have been made by Snelling (643) and Josephs (317) by means of a study of urobilin excretion in the stools. While there was in most cases at some time within the first six weeks of life a definite rise in urobilin excretion, this was rarely excessive and a close correlation between fall in haemoglobin and urobilin excretion was not obtained<sup>1</sup>. On the other hand, there occurs with great regularity, as already pointed out, a fall in reticulocytes to very low values and a later rise coincident with which the red cells and haemoglobin increase.

<sup>1</sup> S. G. Ross reported similar results at the 1936 meeting of the American Pediatric Society.

in value This behavior of the reticulocytes has given rise to the idea that the fall in haemoglobin is a result of relative failure of haemopoiesis, "hypoplasia" resulting from what might be called "unreadiness for life"

It is impossible at the present time to advance any complete explanation of the relation of these phenomena to the fall in haemoglobin There is no reason to look on the fall as pathological One may regard the processes which regulate the level of haemoglobin and red cells as tending to a state of equilibrium which is, as it were, adjusted like a thermostat at a level of haemoglobin that is "normal" for a given set of conditions As long as the haemoglobin lies above this level, there will not only be no stimulus to increased haemopoiesis, but the rate of blood formation may be actually decreased and the reticulocytes be greatly reduced When the haemoglobin falls below the "normal" level, then increased production will take place and the reticulocytes rise Such a hypothesis explains satisfactorily the reticulocyte variations in the first six to eight weeks of life without evoking the doubtful idea of "hypoplasia," but does not advance our understanding of the factors responsible for the regulation of equilibrium

The rôle played by blood destruction remains in doubt Is it part of the normal process of regulation called into play by some factor of which we have no knowledge, or is it to be regarded as pathological? While at the present time we have no answer to this question, there can be little doubt that it takes an important part in the process of reduction of haemoglobin and is probably largely responsible for the rapid rate at which the haemoglobin becomes reduced

We may summarize the probable course of events about as follows: The infant is born with a level of haemoglobin that is above that which is normal for extra-uterine life As a result, all signs of regeneration quickly disappear and the haemoglobin falls to the level which represents the normal equilibrium of infancy In rare cases this fall takes place gradually without the development of "anaemia" (606, 662), but in the great majority the haemoglobin falls to a lower point from which recovery takes place, the so-called "physiological anaemia" This fall to a point below that of normal equilibrium is attended by signs of regeneration, namely the reticulocyte increase of the sixth to twelfth week of life It is highly probable that this rapid

reduction of haemoglobin is caused by the increased blood destruction, and that the excessive fall is due to the fact that there is a lag in the development of equilibrium, i.e. increased blood destruction is slow to be relinquished and increased formation is slow to be assumed

There are several observations that support this explanation (1) In premature babies there is evidence that the rate of blood destruction is relatively greater and more prolonged (Josephs, urobilin determination (317) and van Creveld (135) icterus index remains high for a longer period) (2) In one case studied by Josephs, a fall in urobilin excretion was attended by cessation of the fall in haemoglobin and thereafter a gradual reduction without the development of "anaemia" (3) While there is no close correlation between urobilin excretion and fall of haemoglobin, it was found that in general in those cases with stationary or slowly falling haemoglobin the urobilin excretion tended to be lower than in those cases with rapidly falling haemoglobin (4) There is no evidence of "hypoplasia," for as soon as the haemoglobin falls to the "anaemic" level, reticulocytosis occurs and in those cases in which the anaemic level has been reached very much earlier (anaemia of newborn) reticulocytes appear at that time (5) The delay in assumption of increased haematopoiesis after excessive fall in haemoglobin is well seen in the cases of acute haemolytic anaemia in which it may be a week or more after the onset before the reticulocytes increase significantly in the circulating blood (6) Hampson, (269) from his experience with maternal serum in the treatment of icterus gravis, suggests that the infant in this condition lacks some anti-hemolytic factor contained in the maternal serum. If this is so, then it is quite possible that the increased haemolysis of the newborn may have to be looked upon as at least partly pathological and due to a delay in initiating the manufacture of an antihemolytic substance which during pregnancy is supplied by the mother—part of the "unreadiness for life" and therefore more marked in the premature baby



## FACTORS INFLUENCING THE BLOOD PICTURE DURING THE FIRST TWO YEARS OF LIFE

### INTRODUCTION

Thus far we have considered the newborn period and attempted to discuss the mechanism by which the adjustment of haemoglobin and red cell levels to the normal values of infancy take place. During the newborn period, constitutional or intrinsic factors are dominant and extrinsic factors play little part. As the extrinsic factors, especially those included under infection and nutrition, assume a greater importance with the growth of the child, constitutional factors become relegated to the background, to that vague group comprised under such terms as diathesis, dyscrasia, constitutional tendency.

We know almost nothing of the regulation of blood formation, possibly it is by hormones the elaboration of which is a specific function of certain tissues, possibly the mechanism is simpler. As the term constitution is used it is a pigeon hole in which to place all the facts which rely for their explanation on an understanding of the mechanism of regulation—why one child becomes anaemic when another under the same conditions does not, why one child shows one type of response and another child a different type. Finkelstein writes, (189) "Constitution is regulation, i.e. ability to compensate for disturbances at one point through the initiation of regulatory processes. In a normal child, the processes of regulation occur so promptly and thoroughly that equilibrium follows quickly and at a normal level or only slightly under the normal. In the anaemic there is 'torpor of regulation' as a result of which the equilibrium is delayed and possible only at a lower level."

### A IRON METABOLISM

Our present conception of the relation of iron metabolism or more specifically of iron deficiency to anaemia of infancy rests on certain facts and beliefs which may be summed up as follows —

Milk has an extremely low iron content not more than a milligram per litre and probably less, but varies with the amount of handling it receives between the cow and the analyst. Breast milk likewise contains little iron, probably very little if any more than cow's milk,

though analyses differ on this point [Wallgren (705) (lit), personal observation]

There are deposits of iron present in the baby at birth which are available for haemoglobin formation up to the sixth month of life, i.e. during the period of most rapid relative growth

Anaemia of nutritional origin is rare before the sixth month of life, but thereafter becomes increasingly common

After the sixth month of life as shown in Chart 1 there is a gradual fall in the normal haemoglobin curve. This has been related to the exhaustion of the stores by the end of the sixth month. In babies whose mothers were anaemic during pregnancy, Strauss has shown a greater fall in haemoglobin by the end of the first year.

In the premature baby the deposits of iron are smaller in amount than in the baby born at term, and it is well known that "nutritional" anaemia occurs relatively earlier in the premature, and is likely to be more severe.

Many anaemic babies who have developed anaemia have received an exclusive milk diet. The relation of a milk diet to anaemia is very striking and has for at least twenty-five years been used as the starting point for theories of etiology of nutritional anaemia.

Animals fed an exclusive diet of milk develop anaemia which has been shown to be due to iron deficiency, and which can be cured by the addition of iron to the milk. (Copper must also be added to assure adequate utilization of iron in rats.)

The conception of anaemia of infancy as the result of a deficiency receives support from the fact that there is often a relation between a rapid relative rate of growth and severity of anaemia. Iron is the most obvious deficiency though other deficiencies may contribute (See section on vitamins below.)

The striking effect of iron therapy is one of the strongest supports for the conception of iron deficiency as the principal cause. Among some workers a prompt recovery after administration of adequate iron is accepted as proof that iron deficiency was responsible for the anaemia.

The majority of cases of anaemia are of the chlorotic type which would correspond to what should be expected from iron deficiency.

We may next turn to an examination of these statements in the light

of recent investigation, to learn whether or not we should modify our ideas concerning the relation of anaemia of infancy to iron deficiency. It must be realized that the definitely proven facts concerning iron metabolism are few and that most of our supposed knowledge is inference that has been accepted as fact for so long that it is not appreciated any longer how much of it is not proved.

Although milk contains little iron, recent observations on iron balance indicate that the amount retained by the baby on a diet of milk alone is not negligible (316, 644, 706). During the period of rapid growth it is altogether insufficient to meet the demands of new haemoglobin formation and the infant must rely on stores present in his body at birth or deposited as a consequence of the break-down of haemoglobin that occurs during or shortly after birth. After the sixth month of life the amount of iron retained while somewhat greater is still not quite sufficient to meet the demands for haemoglobin formation, and the baby still has to draw on the iron of the body but to a smaller extent. The fact that the haemoglobin tends to fall somewhat during this period is evidence of the relative exhaustion of these available stores. Recent studies on the quantitative relations between the demand for iron and the available supply have confirmed the preceding statements (316), especially the relative exhaustion of stores by the end of the sixth month. Moreover, histological and quantitative chemical studies have shown that at or shortly after birth there is a relatively large amount of iron in the liver, and that this becomes less after about the first month or six weeks, reaching low and relatively constant values by the end of the first half year of life 10, 226, 254, 618, 680.

**Deficient stores** Since it is impossible in the living baby to analyze tissues for their iron content, all statements regarding the relation of deficient storage of iron at birth to anaemia are the result of inference. There are two types of cases, however, in which the evidence points strongly to deficient stores of iron (680). (a) Strauss 670 has shown that babies of mothers who were anaemic during pregnancy, while born with a normal haemoglobin, tend to have a somewhat reduced haemoglobin at the end of the first year. This relative anaemia in the baby can be prevented by giving the mother iron during pregnancy. MacKay had previously found that babies of mothers re-

ceiving iron during pregnancy tended to have better haemoglobin values than those of untreated mothers (427) (b) Premature babies since the time of Huguenot and Guillemonat have been considered the classical examples of deficient storage. Actually premature babies do not have greatly deficient stores in relation to weight at birth (226, 429, 680), but only in relation to their relatively more rapid gain in weight.

Relation of iron to nutrition anaemia. The evidence on which our present conception of the relation of iron deficiency to nutritional anaemia rests has been given at the beginning of this section. This evidence clearly points to the importance of iron deficiency, but the tendency has been toward overemphasis of iron to the exclusion of other factors. Moreover, the conception of what constitutes iron deficiency is somewhat lacking in definition. (a) Iron deficiency plays no part in the etiology of anaemia in the first six weeks of life and only rarely in the first three months. The anaemias occurring in this period are predominantly of a macrocytic-hyperchromic type. (b) The demonstration by McKay that iron prevented the relatively low haemoglobin in the first six months in her series of babies is offset by the demonstration by Josephs that freedom from exposure to infection can do the same thing. This does not mean that iron deficiency is any less important, but that there are other factors of equal importance. (c) Calculations have shown that a lack of iron in the body by itself cannot account for any severe degree of anaemia (316), even in the premature baby, unless the stores at birth are completely deficient—a condition rare if it ever occurs. Iron deficiency must therefore be dependent either on a net loss of iron from the body or on the deposition of iron in the tissues in a form relatively unavailable. Recent studies (unpublished) have failed to demonstrate a negative iron balance sufficient to cause an appreciable iron deficit. (d) One of the facts leading to the inference in regard to iron deficiency is the frequency of hypochromic anaemia. Hypochromia, however, means no more than deficiency in haemoglobin production and the synthesis of haemoglobin is a complicated process in which an adequate supply of iron plays only a part. Attempts to incriminate the pyrrole ring or some fault in the process of synthesis in anaemia of infancy have thus far been unsuccessful, but one cannot exclude the

possibility that some other factor besides lack of iron may be of significance (e) The anaemia of prematurity, while clearly associated with iron deficiency, is also associated with other factors of importance—constitution as well as repeated infections and nutritional deficiencies (f) Therapeutic effect of iron Iron has two effects therapeutically, it both stimulates haemopoietic tissue and supplies an essential constituent of the haemoglobin molecule The stimulating action of iron while known and discussed for the past forty years, has been definitely demonstrated in cases of human anaemia only recently (313, 330, 461, 529) Some observers notably in England have assumed that a marked response to the administration of iron in any case of anaemia is proof that iron deficiency was the cause of the anaemia in that particular case In one sense that is true but if such a conclusion is applied to other conditions, malaria may be considered due to lack of quinine, or more generally any disease may be due to the lack of something with which it may be cured (g) Animal experimentation The experimental production of anaemia in animals by diets deficient in iron has led to important results particularly in learning the conditions under which anaemia is produced and cured One of the conditions is a rapid relative rate of growth, for it has been shown in rats that as the animal grows on a diet of milk alone the total iron of the body tends to remain relatively constant from the commencement of the milk diet, while the haemoglobin becomes reduced in proportion to the gain in weight (312) Since the rat triples or quadruples his weight in the course of a few weeks the haemoglobin may be reduced to a third or a quarter of its original value—a true iron deficiency anaemia Such a rapid relative gain in weight cannot occur in an infant, so that some caution must be used in applying conclusions reached from the experiments on rats to human pathology

The facts concerning the relation of copper deficiency to anaemia may be briefly stated (h) Copper metabolism i Copper appears to be necessary for the synthesis of haemoglobin in the rat ii Young animals have a higher content of copper than older animals This statement also applies to the infant (338, 526, 567) iii Copper deficiency in the rat can be produced experimentally and probably depends, as in the case of iron deficiency, on the rapid relative growth

of the animal, i.e., dilution of the existing stores until they are no longer present in sufficient concentration to exert their effect. If copper deficiency exists in infants, it is not likely that the mechanism of its production is the same as in the rat. iv Copper is a valuable adjunct in the treatment of anaemia in infancy, but copper deficiency has not yet been demonstrated. v Copper appears to act by catalyzing haemoglobin formation, but only in the presence of an adequate supply of available iron. Administered by itself, copper has no action either on formation of haemoglobin or on the reticulocyte percentage (313, 529).

#### B. PREMATUREITY

The influence of prematurity on the blood in the newborn period has already been indicated. As the infant becomes older he comes under the influence of the usual extrinsic factors, the effect of which appears to be greater than in the case of the full term infant.

There are three phases to the anaemia of premature babies.

a The early "physiological" anaemia differing in no respect except quantitatively from the "physiological" anaemia of full term babies, and undoubtedly due to the same mechanism. During the development of the anaemia there is a failure to react to haemopoietic stimulants, but after about the eighth week iron or liver administration is followed by a reticulocyte rise and a rise in red cells and haemoglobin. There is no evidence that iron deficiency occurs in this early period.

b This early period of physiological anaemia passes into the second period characterized by a continued lowering of the color index due rather to a gradual rise in red cells than to a further reduction in haemoglobin. Recovery during this second phase is rather slow and is often not completed until the second year of life. Reaction to haemopoietic stimuli such as iron and liver is usually good. Extrinsic factors play an important part in this period, especially mild degrees of iron deficiency.

c The third type of anaemia ascribed to prematurity differs in no way from the ordinary hypochromic anaemia of infancy except that it occurs earlier and is likely to be more profound. Since the premature baby is exposed to the same influences as any other baby there have been attempts to blame the early development of anaemia on some constitutional or predisposing factor.

i Iron deficiency From the time of Huguoneng it has been the custom to ascribe the prevalence of anaemia in premature babies to deficient iron storage at birth As has been pointed out above, iron stores, though lower in the premature than in the full term infant (10, 67, 226, 680) may be considered deficient only in comparison with the relatively more rapid rate of growth Iron deficiency probably does not occur before the third month except under abnormal conditions leading to loss of iron such as haemorrhage or possibly excessive haemolysis, and there is no reason to believe that the response to iron administration that occurs at about the end of the second month is evidence of iron deficiency After the third month iron deficiency becomes increasingly important as an etiological factor Although iron deficiency undoubtedly plays a larger part in the etiology than in full term babies, it is not possible to account for any extreme degree of anaemia on the basis of iron deficiency alone We are forced to infer either a failure to utilize iron, or an inability to synthesize haemoglobin sufficiently rapidly Lichtenstein's (408) observation that premature babies had for a time a negative iron balance has not been confirmed by more recent work (644)

ii Constitutional fault in haemopoiesis (7, 32, 202, 519, 644) This is no more than the "Konstitutionelle Minderwertigkeit" of the German literature, too vague a conception to admit of discussion It can neither be proved nor disproved, and until we know more of the factors regulating haemopoiesis such a conception is a not very useful hypothesis

iii Infection As is well known, premature babies are particularly susceptible to infections, especially of the upper respiratory tract This again points to a possible constitutional factor, but we know nothing yet of the mechanism The relation of infection to anaemia will be discussed in the next section

iv Syphilis Syphilis occupies an important position especially in anaemia occurring in the first three or four months of life Syphilis is a cause of prematurity and syphilis is often accompanied by anaemia which may at times be severe

v The greater incidence and severity of deficiency diseases in the premature may be pointed out here The relation of nutritional deficiency to anaemia will be discussed later

It may be seen that the problem of the relation of prematurity to the occurrence of anaemia is a complex one, and, as we shall see in other instances, it is almost impossible to separate out one factor and incriminate that one as the cause of anaemia. We cannot disassociate prematurity from the increased incidence of infections, from the possibility of a deficiency factor, or from any of the hypothetical defects summed up under the term "constitution."

Severe anaemia occurring early in premature babies carries a bad prognosis. This is due not so much to the anaemia as to the underlying factors that render the premature baby's existence precarious even under the best of conditions.

### C INFECTIONS

#### *1 General considerations*

Infections play an important part in the development of anaemia at any age, but especially so in infancy. It is rare at this age to encounter anaemia with a clear cut etiology and generally infections, nutritional and constitutional factors are so inextricably mixed that it is frequently impossible to determine which is predominant in causing the particular clinical and haematological picture that is present. Infection may precipitate anaemia, consequent loss of appetite and the continuation of an exclusive milk diet may prolong the anaemia. But anaemic infants are susceptible to infections and so a vicious circle is established. Anaemia starting as a result of prematurity or on other constitutional grounds predisposes to infection and to loss of appetite, and so again the vicious circle is started.

If we exclude the newborn period, the most important causes of severe anaemia in the first three months of life are syphilis and sepsis (343, 519, 668). As we saw in the section on physiological anaemia it is probable that a mild reduction of haemoglobin may be dependent on mild "sub clinical" infections. At this age, however, constitutional factors are still present in all infants, and for that reason we may see a picture result from mild infections that we would not expect later on. In the second three months of life anaemia is uncommon (668). This appears to be a time of relative immunity to infection. Toward the end of this period we begin to see cases of anaemia now due to combination of infection and nutrition with constitutional factors.



only rarely playing any dominant part. The frequency of upper respiratory infections and pneumonia, as well as nutritional factors, have a bearing on the increasing frequency of anaemia from this time on. As the child grows, however, infections play less and less part, not because they are any less frequent but because as the child becomes older his haemopoietic apparatus becomes more stable, and it requires a more severe or more prolonged infection to produce anaemia. It is therefore between the sixth and eighteenth month of life that anaemia is most frequent.

Individual variation plays a large rôle in the infant's reaction to infection. These little understood factors that form the basis for individual variation are included especially by German authors under the general term "constitution". It must not be forgotten, however, that under these circumstances "constitution" is no more than a convenient pigeon-hole for little understood factors and that the use of the term is merely a name for our ignorance.

In its mildest form infection by itself has little influence on haemoglobin and red cell counts as in the case of the minimal "anaemia" occurring in the first three or four months of life or in premature babies for a somewhat longer period. At most it prolongs a nutritional anaemia, interferes with appetite, temporarily prevents the curative effect of iron, and causes a latent vitamin deficiency to become active. In the more severe acute infections, especially in pneumonia, there may occur considerable reduction in red cells and haemoglobin, but almost never to the extent encountered in cases in which nutritional or alimentary factors are predominant (519, 668, Personal observation). Haemoglobin is rarely reduced below 6 or 7 grams per 100 cc and the red cells rarely below three million. The color index tends to be below one, but extreme hypochromia is rare. Nucleated red cells are uncommonly encountered, reticulocytes tend to be reduced, and administration of iron is not followed by the usual signs of regeneration. Urobilin excretion in the stools tends to be moderately increased (314), so that it is probable that the anaemia depends to some extent on increased blood destruction which is compensated for only at a lower level of haemoglobin. There may be some loss of iron during infections, but it has not yet been shown that the loss is sufficient to account for subsequent iron-deficiency anaemia (316).

After the acute phase of the infection is over, usually the haemoglobin and red cells return relatively quickly to the normal level, but in many cases some form of stimulation, such as is supplied by inorganic iron in adequate doses, is necessary. Finkelstein (189) stresses the point that infection interferes with "regulation" and that iron restores the "regulation" to its normal condition. It has been found in some cases that iron administered after an infection is followed by a rise in reticulocytes and red cells, but that the haemoglobin lags. In such cases, copper may accelerate the haemoglobin formation (313, 529).

In chronic infections of moderate severity the haemoglobin and red cells are often somewhat reduced and it is extremely difficult to raise them permanently by any means. In these cases there is ordinarily no evidence of increased blood destruction and the anaemia appears to be of an aregenerative type.

In the very severe infections represented by sepsis, furunculosis or pyrodermia of small, poorly developed babies, pyogenic abscesses, etc., the reduction of red cells and haemoglobin may not only be severe but qualitative changes in the blood are evidence of the profound damage brought about by the infection. Not all severe infections are attended by these changes and it is an interesting fact that a severe streptococcus infection such as erysipelas may not cause any disturbance whatever.

The type of picture encountered varies with the age of the patient as well as the severity of the infection. In the very young, especially in the newborn period, the reaction tends to be erythroblastic and pseudoleukaemic, while later aregenerative or hypoplastic pictures tend to be more common. Even in the very young, however, aregenerative pictures occur and not infrequently the platelets or white cells may be reduced, even in the presence of erythroblastosis. Such pictures are sometimes classed as "pernicious." Where the hypoplastic picture is present, haemorrhages may occur, although a haemorrhagic tendency is by no means confined to such cases. Frank (202) distinguishes between the effects of pyemia and septicaemia, the former tending to cause regenerative pictures with erythroblastosis, the latter tending to produce a deeper haemopoietic injury with signs of hypoplasia. In older infants and in children erythroblastic pic-

tures may occur but in such cases it is likely that nutritional, gastrointestinal or constitutional factors are also present

Blood destruction is often if not usually increased in these cases but is generally of minor importance compared with damage to the haemopoietic function. While the white cells and platelets are frequently reduced, agranulocytosis or thrombocytopenia as isolated phenomena, as well as aplastic anaemia, are rare occurrences as a result of infection in infancy (See section on Hypoplastic anaemia.)

## *2 Specific infections*

The infections that have been discussed up to this point are those primarily associated with the ordinary pyogenic organisms, those usually found in abscesses, pneumonia, empyema, upper respiratory infections, sepsis, i.e., the organisms responsible for the great majority of the infections of infancy. There are, however, certain other infections that have been specially studied and in which anaemia may sometimes be found, another group in which a more or less specific anaemia may occur and a third group in which anaemia does not occur. Taking up the last group, anaemia does not occur more than to a very minor extent if at all in the ordinary exanthemata, or other contagious diseases of childhood—measles, scarlatina, varicella, mumps, pertussis (unless pneumonia occurs) variola, meningococcus meningitis. It is doubtful if it occurs in diphtheria, although older writers stressed its occurrence in this disease.

Among the infections capable of producing some degree of anaemia are dysentery, pyelitis and tuberculosis, in the group in which anaemia may be part of the clinical picture are congenital syphilis, malaria and kala-azar.

a. *Dysentery and related organisms* Acute dysentery in infancy is almost never accompanied by anaemia unless by coincidence. Chronic dysentery, however, not infrequently produces a moderate or even severe anaemia. This anaemia, however, is of the so-called "secondary" type associated with low color index, and is usually cured by iron medication even while the symptoms of dysentery persist. It is likely, therefore, that the condition is dependent on the chronic gastrointestinal disturbance with difficulty in absorption rather than on the toxicity of the organism. Sepsis due to the related

supestifer organism may occasionally cause a hypoplastic blood picture similar to that in other cases of sepsis, but ordinarily the blood changes of supestifer infection are not of any great importance

b Chronic pyelitis (518, 619, 663) is sometimes associated with anaemia that may be resistant to treatment, but usually is not of very severe grade. Opinions differ as to its importance. Stransky considers it of considerable importance capable even of producing the v Jaksch syndrome, and Kleinschmidt (343) makes the statement that whenever he sees an obscure anaemia in the second half year of life with slight fever he thinks of chronic pyelitis. In Stransky's (668) statistics, pyelitis was a cause of anaemia only between the third month and the end of the first year

c Tuberculosis. A mild unimportant anaemia frequently occurs in tuberculosis, while severe anaemia is exceptional, according to most observers (32, 343, 111). Among the French, however, there is a different point of view and tuberculosis is considered by some authors as one of the more important causes of severe anaemia, (398, 541) but I cannot find any adequate basis in the literature for this point of view

d Syphilis. Anaemia is present in a large proportion of cases of congenital syphilis, especially in the first half year of life, (343, 398, 668) but the relationship is not clear. A fairly large percentage of syphilitic babies are born prematurely or are of low birth weight, many have secondary infections early in life. In the great majority the anaemia is not severe and does not differ from that commonly seen in infancy (501, 685, 752). Successful treatment of syphilis does not cause a cure of the anaemia (201, 295, 661, 723, 754)

From these considerations we may conclude that in many cases syphilis is a factor in the anaemia, but an indirect one by causing prematurity, predisposing to infections or in other ways interfering with the proper development of the infant, but that there is no evidence from these cases that syphilis in itself causes anaemia

There are, however, other cases in which the anaemia is much more severe and in which syphilis appears to play a much more direct rôle, and it is these that most authors have in mind when they write of syphilitic anaemia. Stransky (668) gives syphilis an important place in the anaemias of the first three months, Kleinschmidt (343) states

that he considers syphilis first when he encounters anaemia in the first half year, and in the great majority of reports of severe anaemia in congenital syphilis the babies are under four months of age. Judging by the scarcity of reports, severe anaemia in syphilis in this country must be less common than these statements would indicate. My own experience in looking for syphilitic anaemia during the past five years has convinced me of its rarity at this clinic, although mild anaemia is common enough in syphilitic babies.

The haematological picture in the severe cases is similar to that of sepsis, with all gradations from a simple reduction of red cells to an extreme erythroblastic and pseudoleukemic picture and less commonly an aregenerative blood picture (295, 333, 388, 556, 619, 661, 662, 664, 723, 714, 752). As in sepsis, the platelets may be reduced even in the presence of an erythroblastosis (434, 684, 752). Leucopenia may occur rarely, and occasionally a picture has been described as "pernicious" in type (752). As in most cases at this period of life, the anaemia tends to be macrocytic and hyperchromic. Haemorrhage may occur, and syphilis is a not uncommon cause of haemorrhagic disease of the newborn.

As may be seen from this description, the anaemia of syphilis is in no way specific and the frequent presence of severe infections in the severe syphilitic cases renders interpretation often difficult. Kleinschmidt, Frank and Stransky have all stressed the occurrence of visceral lesions in cases of marked anaemia, osseous lesions being included under the term "visceral," and McLean (433) calls attention to the fact that in his cases severe anaemia was associated with marked osseous lesions (x-ray). On the other hand, widespread bone involvement may be present without anaemia (433, 681). The persistence of extramedullary foci of haemopoiesis characteristic of congenital syphilis would seem to have some relation to the tendency to erythroblastic pictures, but no basis for such a relationship has been found in observed cases. We have seen two cases, however, that are interesting from this point of view. In both there was marked erythroblastosis and increase in lymphocytes with reduction in granulocytes and platelets, the urobilin excretion was low, suggesting an aplastic anaemia. At autopsy the bone marrow was found converted into syphilitic connective tissue, and there was an extremely widespread extramedullary haematopoiesis. In one of these cases there was a

terminal staphylococcus septicaemia which renders interpretation difficult

c Malaria Malaria need only be briefly considered There is very little in the literature on the peculiarities of the anaemia of malaria in infancy, no more than a few case reports (37, 65) In Italy the interest in malaria of the newborn period has centered mostly in the question of prenatal transmission and not in the blood picture Jemma, (307) in an article on malaria in children, merely states that the blood changes are greater in children than in adults and come on sooner (103) The picture tends toward erythroblastosis and pseudo-leukaemia with occasionally one that might be called pernicious, which means the presence of megaloblasts, a leucopenia and possible thrombopenia Malaria has been reported in the newborn period as the result of placental transmission (20, 195, 403), also following transfusion or injection of blood (172, 305, 731) In two of these cases a picture of erythroblastic anaemia was present in the second month of life The rarity of malaria in infancy is shown by Belajeva (48) who found no cases under two years of age in a series of 119 cases in childhood

f Kala-azar Kala-azar or Leishmaniasis is rare except in tropical or subtropical countries especially Italy, southern France (about Marseilles) and China The anaemia is of hypoplastic type with leukopenia and increase in monocytes It occurs primarily in early childhood and has been thoroughly studied in Italy and by Giraud in France (96, 223, 224, 306, 439, 447)

#### D VITAMINS

The association of anaemia with diseases due to vitamin deficiency is a frequent observation, but it is not easy to determine the relation between anaemia and any specific deficiency The occasional case in which the relation of cause and effect can be demonstrated does not permit any such generalizations as one frequently encounters in the literature On the other hand statistical proof which would allow generalization has not yet been brought in any instance The difficulty rests in the number of possible collateral or intermediate relationships

(1) In the feeding of infants, diets deficient in one vitamin are often deficient in others as well as in iron

(2) In ordinary times vitamin deficiencies are usually encountered among the poor and ignorant among whom anaemia is likely to be more common

(3) In the period of post-war inflation in Germany, the incidence of anaemia and of deficiency diseases showed similar curves as was pointed out by Aron (23) While this makes an excellent demonstration of the association of anaemia and deficiency disease, it is no proof that vitamin deficiency was the cause of the anaemia, or that outside of such periods there will be such a close relationship between food deficiencies and anaemia

(4) Premature babies, twins, and others of low birth weight are particularly liable to both anaemia and deficiency disease

(5) Chronic gastrointestinal disease leading to failure of absorption, may be the fundamental cause of both a vitamin deficiency and anaemia In celiac disease and chronic bacillary dysentery both of which are frequently associated with vitamin deficiency especially scurvy, the anaemia is ordinarily of the hypochromic type readily cured with large doses of iron Moreover, as has been shown in sprue, lack of some nutritional factor closely associated with vitamin B<sub>2</sub> can cause a chronic nutritional disturbance with consequent poor absorption and so establish a vicious circle

(6) Vitamin deficiency may predispose to infection and so be an indirect cause of anaemia and on the other hand an infection may render a "latent" deficiency clinically active and at the same time precipitate an anaemia

In the following section will be presented the evidence for or against a specific relationship between vitamin deficiency and anaemia

### *Vitamin A*

From the few observations on the blood in cases of xerophthalmia that are to be found in the literature, there is no evidence that vitamin A has any direct influence on blood formation (204, 331, 359, 617, 628) In cases in which anaemia was present there was always some associated deficiency or gastrointestinal disturbance (331) In Blackfan and Wolbach's (63) cases in infants, most of whom suffered from A deficiency in an early stage before the development of xerophthalmia, anaemia was no more common than it would have been in a similar group suffering from nutritional disturbances and infections.

Sweet and K'ang (675) conclude that vitamin A does not by itself produce anaemia, basing their conclusions on a large series of cases studied in China

### *Vitamin B*

Uncomplicated beriberi is not associated with anaemia (331, 693), so that we may exclude vitamin B<sub>1</sub> as a cause of anaemia

Evidence connecting vitamin B<sub>2</sub> with macrocytic anaemia may be summed up as follows

(a) Pellagra (686, 190, 68) While anaemia occurs in pellagra it is only in rare instances of a specific macrocytic type The characteristic gastro-intestinal disturbance of pellagra with consequent failure to absorb is the probable cause of the anaemia as in celiac disease or sprue The particular factor of the B vitamin, the lack of which is responsible for pellagra probably has no direct influence on the blood

(b) Castle (100) has recently summed up the evidence for the relation between vitamin B<sub>2</sub> and macrocytic anaemia of sprue, pregnancy and celiac disease reaching the conclusion that while there was an association between the "extrinsic factor" and vitamin B<sub>2</sub>, (52, 653, 671, 693, 697, 734), there was no proof of identity

(c) Parsons, (528) basing his hypothesis on experimental work on rats, suggested that some cases of anaemia in the newborn might be dependent on a lack in the diet of the mother of some substance present in yeast Van Creveld (136) has recently reported a case which supports the possibility of such a relationship Except for these two reports, there have been up to the present no grounds for connecting anaemia of the newborn with a dietary deficiency in the mother

(d) The idea that goat's milk anaemia might be a deficiency disease seems to have originated with Aron (21) in 1922, on the grounds that the cream of goat's milk contained no color Baar (29) found that he could cure goat's milk anaemia by increasing the amount of goat's milk The peculiarities of the blood picture and its similarity in many points to that of pernicious anaemia has been frequently pointed out, (35, 227) especially by Gyorgy (259), who also showed that goat's milk anaemia could be cured by liver or yeast extract Rominger (581) was able to produce a hyperchromic anaemia in rats by feeding goat's milk and showed that this was a form of anaemia dis-



tinct from the usual nutritional anaemia of rats and could be cured by liver but not by vitamin C or iron. This work has been partially confirmed by Haase (262) who also claimed that milk from goats whose diet contained extra amounts of vitamin B did not cause anaemia in his rats. Up to the present this important observation has not been confirmed.

### *Vitamin C*

Recent observations have shown that deficiency of vitamin C<sup>2</sup> can cause an anaemia which is specific in the sense that there occurs after administration of orange juice alone a rise in reticulocytes and a rapid return to normal of the red cells and haemoglobin (314, 443, 462, 529, 533). In the majority of cases in infants in which both scurvy and anaemia are present, however, orange juice has no such effect, and the anaemia is cured in the usual way—by iron in adequate doses (579, Personal observ.). If vitamin C is necessary to complete maturation of the red cells as Witts (740) claims, it is difficult to account for the lack of a specific anaemia in cases in which deficiency of vitamin C is evidently present. It must be remembered that the relation between scurvy and anaemia is much clearer in adults than it is in infants. To account for this discrepancy in behavior several possibilities offer themselves. (1) In the infant the grade of deficiency necessary to produce the pathological changes of scurvy may be less than that necessary for the specific anaemia. (2) The distribution of vitamin C may be uneven with greater concentration in blood forming organs in infants. (3) Vitamin C may be made up of more than one fraction.

The fact that a deficiency of vitamin C is capable of causing a specific damage to the blood forming tissue, does not account for the great majority of cases in infants in which there is no such specific damage. There is ordinarily no relation between the severity of the signs of scurvy and the severity of the anaemia. The half dozen cases of proved vitamin C deficiency anaemia are insufficient for any

<sup>2</sup> It must be understood that vitamin C as used in this work does not mean cevitic acid or ascorbic acid. It is for the future to determine whether the conception of vitamin C that has prevailed up to the present is to be satisfied by a single pure crystalline substance, or whether more than one will be necessary.

generalization as to type. In these cases the color index tends to be around one, (314, 462, 228) or somewhat below, and the red cells are about normal in size. Apart from these few cases, the anaemia associated with scurvy may be of any type, but is usually hypochromic in infancy (533, 579, Personal observ.) The fact that reticulocytes are not increased argues against increased hemolysis. The haemorrhages of scurvy are rarely sufficient to account for anaemia, and moreover there is no relation between haemorrhagic tendency and anaemia in scurvy. Bone marrow injury has been generally accepted as the underlying cause, but the older idea that this was dependent on the scorbutic bone changes is being abandoned in favor of a specific injury from vitamin C deficiency, although as we have seen, the evidence for this rests on half a dozen cases, and there are discrepancies which have not yet been explained.

### *Vitamin D*

The frequent association of rickets and anaemia originally gave rise to the idea that anaemia, especially the "von Jaksch" type might be due to rickets. This hypothesis is now being gradually abandoned, in favor of the idea that rickets and anaemia are each due to causes that are often associated (43, 189, 343, 429, 443, 519, 529, 628). It has been abundantly shown that rickets and anaemia may be cured independently of each other by appropriate treatment, and that there is no relation between the severity of the anaemia and of the rickets. It must be remembered, however, that failure to demonstrate a relationship does not mean that a relationship may not exist. It has proved impossible in clinical work to control all the factors that might interfere with interpretation. Animal experimentation, with its greater possibilities of control, has given results no more favorable to the idea of some relation between vitamin D deficiency and anaemia but results obtained in animals should be applied to the solution of human problems with caution.

Marfan claims to have found the relationship in the infections or intoxications that on the one hand destroyed vitamin D and on the other caused anaemia. L. Weill (720) reviewed the French literature very completely and from it concludes that rickets has no direct influence on the development of anaemia.

## E POISONS

The only poisoning of any importance in infancy causing changes in the blood is that produced by lead if we except the occasional results from arsphenamine in the treatment of syphilis. Lead poisoning in infancy is however uncommon except in Japan where it is due to the use of cosmetics containing lead. In this country and in Europe it has occasionally been reported following the use on the nipple of lead washes. In Baltimore recently the use of storage batteries for fuel resulted in an "epidemic" of lead poisoning. Compared with the public health aspects and the severity of the disease, the problem of anaemia is a very minor one. The red cells rarely fall below three and one-half million or the haemoglobin below 50 per cent. There is an increase in reticulocytes that very roughly parallels the severity of the anaemia, (210, 235, 326) nucleated red cells are frequently present (210, 235, 326) and may occur even in the mild cases (658, personal observation). The percentage of stippling in the red cells likewise parallels the severity, but its variability and the fact that basophilic stippling is not infrequently encountered in infancy at any time when blood regeneration is occurring lessens its value as a diagnostic aid.

The absence of anaemia of more than relatively mild degree is probably due to the acuteness of the course which either terminates fatally in a short time from central nervous system involvement before the blood can be much affected, or else leads to early recognition and elimination of the source before further damage is done. It is only occasionally that the question of lead poisoning arises in relation to the problem of determining the cause of obscure anaemia.

## F HAEMORRHAGE

Except in the newborn period haemorrhage sufficient to cause any severe degree of anaemia is uncommon in infancy. A tendency to bleed is encountered in many cases belonging to the haemolytic-erythroblastic group of anaemias manifested by petechiae, or occasionally larger subcutaneous haemorrhages and retinal haemorrhages but rarely by frank bleeding sufficient to influence the haemoglobin. This type of purpuric manifestation is in most cases probably dependent on the underlying condition such as infection or possibly scurvy.

in some cases, which increases capillary permeability, rather than on platelet reduction. In some cases of sepsis, however, especially those associated with "hypoplastic" picture, death may result from a profuse haemorrhage or from the slow oozing of small lesions. Occasionally mild infection may be accompanied by isolated purpuric manifestations as in the case reported by Gutfreund (257). Such cases are common enough later on and are usually classed under some such name as symptomatic purpura haemorrhagica. Wolff (741) reported a case occurring in what was diagnosed as paratyphoid B sepsis, and reviewed similar cases in the literature. It is possible that some of these were instances of *supestifer sepsis*. Thrombopenic purpura has also been reported following vaccination in infancy (156, 294, 503).

Apart from such cases, thrombopenic purpura is not common in infancy. In the newborn period it has been reported a number of times, but it must be remembered that platelet reduction has been found also in babies otherwise normal. It has also been reported a number of times beyond the newborn period.

Gastric or duodenal ulcers may occasionally be responsible for haemorrhage sufficient to produce anaemia. These are nearly all in marantic babies and are often associated with infection. In *melaena neonatorum* the bleeding has in a number of cases been associated with gastric or, more commonly, duodenal ulcer.

#### G TUMORS

Little attention has been paid to the anaemia that accompanies malignant tumors of infancy and childhood, partly because it is of minor importance compared with the tumor itself, and partly because the blood changes rarely contribute to the diagnosis of the tumor or are sufficiently characteristic to catch the attention. Because there is no basis in the literature for thus slighting the anaemia of tumors except unsupported statements in the text-books and the various articles on tumors, it seemed proper to take up in some detail the effect on the blood of the tumors most commonly encountered in infancy and childhood. (This is not intended to be a complete study, for I have merely collected a sufficient number of cases to establish the blood picture for each particular type of tumor, and I have not searched the literature nor consulted journals that were not easily available.)

TABLE 1  
*Neuroblastoma*

	AGE	ORIGIN	DURATION BEFORE EXAMINATION	BLOOD				METASTASIS		
				Red blood cells $\times 10^5$	Haemoglobin	White blood cells $\times 10^3$	Smear	Bones	Liver	Other
Matzdorf Askin and Geschikter	12d		1m	6 9	106	18		0	+	
	3w	Adrenal	From birth		68	19 6	Normal	0	+	Other adrenal
v Veen	18d	Adrenal	From birth	3 5	90	21	Normal	0	+	0
	5w	Liver	From birth				"No anaemia"	-	+	0
Kwartin and Twiss Carter	3m	Adrenal	6w	3 3	44	11	Normal	0	+	Pancreas, testicle
	5m		8w	3 4	70	13		0	0	Skin
Gesler u Schein Askun and Geschikter	6m	Adrenal		2 7	47	27	Erythroblasts	0	+	0
	12m	Adrenal			45	21	Normal	0	0	Lymph nodes
H L H 86632	14m	Adrenal	6w	2 9	48	15	Normal	+	+	Pancreas
	15m	Adrenal	3w	2 9	56	4 3	Neutropenia	+	+	Pancreas
Brauthwaite	16m	Adrenal	7w	1 5	25	4 4		+	+	
	16m	Adrenal	4w	3 4	48	7 9	Lymphopenia	+	0	Lymph nodes
Askun and Geschikter Carter	16m	Adrenal	3w	3 4	33	23	Erythroblasts	+	+	Kidney
	17m	Adrenal	2m	1 8	30	27	Normal	+	+	
Askun and Geschikter Kwartin and Twiss	18m	Adrenal		3 6		18 0		0	+	Lungs
	19m	Adrenal	2w	2 8	39	5 0	Normal	-	+	
Carter	21m	Adrenal	2w	4 6	70	15	Normal	+	+	
	23m	Adrenal	4w		40	17	Normal	0	+	0

Askun and Geschlechter	26m	Adrenal	6w	30	20	Myelocytes 8 per cent, erythroblasts	+	+	Lymph nodes
Peters and Horn	2y	Adrenal	3½w	3 3	6 8	Normal	0	±	0
Klein	2½y	Adrenal	7w	1 2	8	Neutropenia	++	+	Lungs, spleen
Karelitz	2½y	Sympathetic chain	10w	1 3	15	Neutropenia, thrombopenia, erythroblasts	++	0	Pancreas, brain
Hoffman	3y	Hypogastric plexus	6½w	2 3	9	Neutropenia, thrombopenia, erythroblasts	+	±	Testicle
Askun and Geschlechter	3y	Adrenal	3m	1 0	9 5	Normal	++	-	
Meyer	3y	Adrenal	2½m	2 0	7 8	Lymphopenia, erythroblasts	++	0	Lymph nodes
Kwartun and Twiss	3y	Adrenal	1m	"Progressive anaemia"			++	-	Pancreas
H L H 84927	3y	Adrenal	3w	3 6	11 6	Normal	-	-	
Maldague	4y	Adrenal	5m.	3 0	11	Normal	+	0	
Rupilius	4y	Adrenal	6w	3 6	35	Neutropenia	+		
Volpe et Bloise	3y	Adrenal region	3m	2 0	4 8	Neutropenia	++	+	Lymph nodes
Volpe et Bloise	4y	Adrenal region	3m	3 1	9	Neutropenia	+	+	
Askun and Geschlechter	4y	Adrenal	8m	1 2	10	Lymphopenia, erythroblasts	+	0	
Askun and Geschlechter	5y	Adrenal	4m	2 2	7 1	Normal	+	0	
Eckardt	5y	Adrenal	2w	5 1	15 3	Normal	0	0	
Mfeuner	6y	Adrenal	4m	2 9	4 6	Neutropenia	++	0	
F P Weber	5y	Adrenal	6w	3 8	18	Neutropenia	++	0	0
	5y	Adrenal	4½m	2 7	35	Neutropenia	++	+	
	5y	Adrenal	7m	1 3	11 6	Normal	+	+	Ovary
	5y	Adrenal	4m	1 1	1 3		+	+	

The tumors most commonly encountered in infancy and childhood have been divided into groups —(1) neuroblastoma, (2) tumors of the kidney, (3) lymphosarcoma, (4) a miscellaneous group comprising sarcomata arising in retroperitoneal tissues, intestines, bone, etc

1 *Neuroblastoma* (table 1) This is one of the most common of the malignant tumors of infancy, occurring predominantly in the first three years of life. It usually arises in one of the adrenal glands and is characterized by its great malignancy, metastasizing early to the liver and bones, especially those of the skull. Two types are distinguished clinically (1) the "Pepper" type occurring predominantly in infants with metastases to the liver which may occur so early that the enlargement of liver is the only sign, though usually an abdominal tumor is also present. Metastases to bones rarely occur in this type, (2) the "Hutchison" type with metastases to the skull, especially the orbit, giving rise to a characteristic clinical picture. In these cases an abdominal tumor may occasionally be absent, and the condition must be differentiated from chloroma. In diagnosing these two conditions the blood picture can be of considerable help. *Metastases to the liver* are common in the "Hutchison" type, but rarely occur to the same extent as in the "Pepper" type of infancy. *Metastases to bones other than the skull* are common and probably occur more frequently than they have been reported, owing to the usual failure to search for them. Other metastases occur especially to regional *lymph-nodes* and *pancreas*, but they are inconstant and are of little importance to the present discussion.

Anaemia is associated with neuroblastoma with great frequency and is often profound. It is less severe in the younger patients than in the older ones with bone metastases, and has not occurred in the cases occurring in the first six weeks of life. The most obvious explanation of the severity of the anaemia lies in widespread involvement of the bone marrow, though it must be admitted that in the cases with the severest reduction of red cells, evidence for widespread involvement has not always been found in the case reports.

The anaemia is generally of the common hypochromic variety usually designated "secondary," but, in the older children especially, it may be frequently hyperchromic with great reduction of red cells. The *white count* is usually slightly raised, reaching figures above

20,000 three times and only in infants. In a few cases there was leukopenia. *Neutropenia* of a mild degree occurred in a number of cases associated usually with marked bone involvement. *Platelets* in the few cases in which they have been noted have been found "normal" in numbers even when the neutropenia was observed. Haemorrhagic tendency has not been encountered. Normoblasts have occasionally been found, as have also myelocytes, but never in excessive numbers. Lymphoblasts or myeloblasts have not been present in any case in this series.

2 *Kidney tumors* (308, 368, 649, 672, personal observation). These are predominantly of the type known as "mixed-cell sarcoma" or "Willm's tumor". Metastases tend to occur late and almost never are found in the bones. The liver and lungs are frequently involved together, the former usually by direct extension, the latter through the blood stream. Anaemia when it occurs is seldom of great severity as compared to the anaemia of neuroblastoma, the red cells rarely going below three million and the haemoglobin rarely below forty-five per cent. The severity of the anaemia appeared to bear no relation to age, duration or presence of metastases.

3 *Lymphosarcoma*. This tumor uncommon before the third decade of life has been reported but rarely in infancy (548, 212). Anaemia or other blood changes are not ordinarily part of the clinical picture as given in the ordinary accounts which are mostly based on experience with adults. From the available cases (160, 246, 478, 489, 507, 620, 212) (i.e., reports of cases in which blood studies have been included) it appears that anaemia may be fairly frequent in childhood, but has no characteristics that are helpful in diagnosis. Bone involvement occurs in a small proportion of cases and according to Naegeli anaemia may be severe in these cases. Evans and Leucutia report three cases in adults in which bone involvement was accompanied by a change in the blood picture to that of leukemia. Landau reports the same occurrence in a child. The occurrence of leukaemic blood pictures as a terminal event in lymphosarcoma has been the subject of much discussion (117, 345, 491) which need not be repeated here. At the present time the tendency is to regard such cases as leukemia in which the pathological process tends to remain local for a time without giving rise to blood changes, and so leading to



a faulty diagnosis of lymphosarcoma. It is probable that in these cases a careful examination of the blood smear would reveal abnormal cells that should at least arouse the suspicion of leukemia even though a diagnosis would have to wait for further developments.

4 *Sarcoma* in general is not associated with any marked degree of anaemia. This was very evident on going over the material available in the records of the Harriet Lane Home and was confirmed by a review of the literature. Since this appears to be the general view expressed in many accounts of the subject, it has not seemed worth while to cite references for the statement. In the case of sarcoma involving bone, however, it has seemed profitable to go into more detail, for *a priori* one might expect any widespread involvement of marrow spaces to be accompanied by changes in the blood characteristic of marrow replacement such as often occur in osteosclerosis.

As long as the bone tumor remains localized there is in general no anaemia. In the terminal stages, however, anaemia may be severe and is then associated with widespread skeletal involvement. But even in such cases the characteristics of the blood picture are not those that one usually associates with extreme replacement of marrow tissue, but rather an accompaniment of a general failure of function associated with cachexia (71, 218, 355, 356). Even when the skeletal involvement is extreme there may be no anaemia worthy of the name. Hassler and Krauspe's case with terminal erythroblastosis, neutropenia and thrombopenia is rare enough to stand out as an exception.

Widespread involvement of bones is rarely encountered in infancy and early childhood. We have seen this fact substantiated in the case of neuroblastoma in which bone metastases are rare before two years of age. Whether or not the bones of infants are in general immune to primary and metastatic tumors it is difficult to say, for except for neuroblastoma and mixed sarcoma of the kidney malignant tumors are exceedingly rare in infancy. I have been able to find only three cases of generalized bone involvement in infancy reported by (1) A. R. Meyer (three years, no anaemia), (2) Sevier (eighteen months rapidly developing anaemia coincident with skeletal metastases), (3) Hassler and Krauspe (eight months erythroblastosis, neutropenia and thrombopenia).

Tumors arising from cells of the bone marrow are likewise rare in infancy. Multiple myeloma is usually considered not to occur in

childhood but there have been a number of reports of cases of tumors with multiple bone involvement which have been considered at least closely related to myeloma. Roman two cases called myeloblastic sarcoma [(1) two years, r 14, h 16 per cent, w 88, neutropenia, (2) three years, r 13, h 20 per cent, w 33 with 10 per cent neutrophiles] Berkheiser (three and a half years, r 35, h 40, w 70) Kunstadter "myelosarcomatosis" (six years, r 26, h 50 per cent, w 6-12 with some tendency to immaturity and the presence of erythroblasts) Slavik (eight months "anaemic") Slavens (four years, no anaemia) Mezov (eight months "anaemic") The nature of these cases is in doubt, but it is not unlikely that some at least represent an unusual form of xanthomatosis or related condition. A case reported by B. M. Joseph possibly belongs in the same category.

Chloroma is a form of leukemia with characteristic involvement of the periosteum especially of the skull, and with invasive tendency. In this sense it is analogous to Sternberg's leukosarcoma. The reason for considering it here is that it behaves clinically like a malignant tumor with metastases to bones. A frankly leukemic blood picture is sometimes absent (101, 354, 493, 524, 544, 583) but even in such cases there are usually a number of immature forms sufficiently abnormal to arouse the suspicion of leukemia. Nucleated red cells are usually present but rarely in large numbers.

The classical picture of chloroma need not be repeated here, it may be found in any book on hematology and in recent articles by Feer and Washburn in which special problems are discussed. It has been reported a number of times in infancy (101, 182, 455, 493, 674). In Washburn's case in which recovery took place following radiation, there has recently been raised a question as to the correctness of the original diagnosis of chloroma (personal communication).

## H GASTRO-INTESTINAL DISTURBANCES

Acute gastro-intestinal disturbances are rarely if ever a factor in the anaemia of infancy. Chronic disturbances on the other hand may be not infrequently associated with anaemia, but the type of chronic disturbance which is associated with anaemia is relatively rare in infancy. There are, however, certain conditions that deserve special mention in a discussion of anaemia of infancy.

1 *Celiac disease* Because of the many points of similarity be-

tween celiac disease and sprue, there is considerable interest in the fact that a macrocytic, hyperchromic anaemia has been reported a number of times in "celiac" disease, and that in some cases the haematological picture has approached that of pernicious anaemia (179, 280, 282, 301, 529, 587, 697, 699) That these cases of macrocytic, hyperchromic anaemia are exceptional appears from the recent work of Neale, Smallwood and Shippam (497) both from reviewing the literature and from their own observation Typical celiac disease is, however, uncommon in infancy, and although it may often be a question of nomenclature whether we include a given case under this diagnosis or under chronic nutritional disturbance, the fact remains that the macrocytic hyperchromic anaemias have been almost exclusively encountered in older children and adults In infancy the usual type of anaemia associated with chronic nutritional or gastrointestinal disturbance is hypochromic, (179, 280, 529) though occasionally there may be present hyperchromia (653) In a few cases in infancy there may develop an erythroblastic type of blood picture (v Jaksch syndrome). Fanconi states that the von Jaksch picture tends to occur in the younger children while pernicious pictures occur only in older patients, but the dividing line between the von Jaksch picture and the pernicious picture is not always a sharp one as we shall point out later. The erythroblastic picture has also been described in adults (52) Stanqvist (652) reported a case with severe anaemia and tendency to haemorrhage

The factors that enter into the etiology of the anaemia are somewhat complicated At the present time it is believed that relative failure of absorption plays a large part in the symptoms of celiac disease This might lead to deficiency of available iron and so to the development of a hypochromic anaemia Vitamin deficiency diseases are not uncommon occurrences in the course of celiac disease, and these children are particularly susceptible to infections The presence of a macrocytic anaemia and its cure with yeast and yeast extracts suggests a deficiency in Castle's "extrinsic" factor as has been discussed above (section on Vitamins—Vitamins B) Finally Fanconi reported some cases in which the chronic gastro-intestinal disturbance cleared up following the successful treatment of the anaemia with iron

2 *Goat's milk anaemia* The distinction between goat's milk anaemia and cow's milk anaemia while bad from a logical point of view, since it implies something of which there is no proof, is useful clinically. One of the chief differences in the clinical pictures is that babies who have the anaemia that has come to be considered characteristic of goat's milk tend to have a more or less chronic diarrhea often reminiscent of that of celiac disease and are usually poorly nourished and poorly developed (79, 227, 259, 668)—what in Germany, whence come most of the reports, is called "dystrophy"—while the babies developing anaemia on cow's milk are more likely to be constipated and are generally in a better nutritional condition. The anaemia that has come to be considered characteristic of goat's milk feeding is of a type described by Gyorgy and others before him as pernicious (35, 227, 259, 588). The distinction between what some call "pernicious pictures" and others call the "v. Jaksch picture" is not clear, and will be discussed later. It need only be pointed out here that certain characteristics of pernicious anaemia occur following the feeding of goat's milk in association with a more or less chronic gastro intestinal disturbance. The reasons for believing that these cases are due to a deficiency of "extrinsic" factor have been given previously (section on Vitamins—Vitamin B). It must, however, be noted that the relation of cause and effect between the blood picture and chronic gastro-intestinal disturbance is not clear and in many if not the majority of cases the development of anaemia appears to have antedated the diarrhea.

3 *Gastric acidity* Of late years increasing interest is being taken in gastric analysis in relation to the anaemias of infancy. Up to the present, however, there are too few determinations by the more recent methods—alcohol test meal, histamine stimulation and fractional analysis. In general, in normal infants the secretion of HCl is lower than in older children or in adults (34, 109, 176, 344, 476, 495, 625, 654, 657). It is reduced below the level normal for the age by infections and gastro-intestinal disease (142, 451, 748). Gastric analysis in anaemia has given discordant results, but enough has been learned to indicate that this procedure is not very useful in the clinical differentiation of the various types of anaemia. In the hypochromic anaemias *Hawskley and Lightwood* (280) found HCl deficit in all the

cases examined, and in two cases in which subsequent determinations were made achlorhydria persisted after the anaemia was cured *Ogilvie* found achlorhydria in only two of nineteen cases while in twelve of the nineteen cases the HCl was considered within normal limits though the lower limit of normal was less than is usually considered normal in adults *Faber* and his co-workers found low HCl in 10 cases examined The interest in these figures and in the "normal" low figures rests in the possibility that iron deficiency anaemia may depend to some extent on a failure to absorb iron consequent on the low acidity Such an inference is highly hypothetical and it is impossible to test it by observation until some method is devised for studying iron absorption

HCl deficit has also been found in congenital haemolytic jaundice (512), Mediterranean anaemia (353, 725), sickle cell anaemia (715), von Jaksch syndrome (512), celiac disease with hyperchromia but no anaemia (653), goat's milk anaemia (259), (one of four cases) and anaemia of hook-worm disease (574) (It is not profitable to give the figures here, as the figures vary according to the method used, and the method has varied with each investigator)

4 *Intestinal parasites* Worms, except for tropical and subtropical regions and certain other parts, are a rare cause of anaemia in children *Ascaris* is practically never a cause, although there are occasional reports in which ascaris infestation and anaemia occur together (339, 130) Mathieu reports a tribe of Arabs given to eating dirt for religious purposes among whom over fifty per cent of the children were infested In cases in which ascaris infestations alone was present there was almost no anaemia, while severe anaemia occurred only in cases with multiple infestations *Trichocephalus dispar* (*trichurus trichura*) has been not so infrequently reported as a cause of anaemia in children but only rarely in infancy (339, 523, 668) The anaemia, when it occurs, appears to be due to the slow blood loss (339, 523), but chronic gastro-intestinal disturbance that accompanies the infestation may have some part in the etiology (184, 237, 420, 679, 702). A recent survey of school children in an endemic focus in Louisiana failed to demonstrate anaemia was any more common in carriers of the worm than in those not harboring it (523) *Taenia solium* and *taenia saginata* have not been reported to cause anaemia *Diphyl-*

*Isotherium latum* infestation, as is well known, occurs with frequency on the Baltic coast where anaemia of a pernicious type occurs in about one of every five thousand carriers. The infestation occurs in this country among Finns in whom it has caused anaemia. It has also occurred in other than Finns, especially in Jewish people in Brooklyn, but has not been associated with anaemia.

The only intestinal parasite that practically need be considered as a cause of anaemia in this country is the *hook-worm*. Cases in infancy, however, are not common since in the first place the opportunities for infestation are rare at this age, and in the second place a certain amount of chronicity is necessary for the development of anaemia. The anaemia of hook-worm infestation is of the hypochromic type usually described as "secondary (331, 574)". It responds to iron even in the presence of the worms (331, 574), but responds only slowly after removal of the worms if iron is not given. There is no conclusive evidence that there is any specific substance associated with the parasites capable of depressing the bone marrow or causing hemolysis (197, 574), and the present conception is that the anaemia is due to chronic blood loss (197, 500, 722, 574), though the severity of the anaemia does not always run parallel with the severity of the infestation (126, 519, 637). It is of course possible that chronic gastrointestinal disturbance may play a part in the etiology (331, 574, 724). Gastric anacidity is a frequent finding. Experimentally, it has been shown that hook-worm infestation in dogs is much increased and the haemoglobin is lower in dogs receiving a deficient diet (197). It has also been observed clinically that the severity of anaemia was greater in the poorly nourished. Chandler stated his belief that the anaemia was due to a specific injury to the bone marrow caused by some substance derived from the worm, but those who have made special studies of the blood do not share this view (574).

5 *Pancreatic disease* Brugsch (82) has recently called attention to the presence of a macrocytic anaemia associated with chronic pancreatic disease in adults. As far as I am aware this association has not been described in children. The reason for the association has not been determined, but it is not unlikely that liver injury is an intermediate factor. "Cysts" of the pancreas have been described in infants especially in connection with vitamin A deficiency (63, 89,

TABLE 2  
*Cirrhosis of the liver*

	AGE	DURATION	HAEMORRHAGE	LIVER	SPLEEN	BLOOD				
						Red blood cells	Haemoglobin	White blood cells	Color index	
H L H 76403	2w	2+w	0	++	+	4 3	95	11 4	1 11	Normal
Paschke	5w	5w	0	+	0	3 5	70	35	1 00	Platelets reduced, erythroblasts
Rosenbaum	6w	6w	0	+	+	2 8	70	29	1 25	Lymphocytosis
Bossert	11w		0	+	+	2 2	75	7 7	1 7	
Lindemann	5m	5m	0	+	+	4 0	74	21	0 93	Lymphocytosis
						2 4		1 4		
H L H 82971	5m	5m	0	++	+	3 2	68	21	1 06	Normal
H L H 91067	7m	7m	0	++	+	3 4	67	18	0 99	Lymphocytosis
de Lange	7m		0	+	+	4 0	83	10	1 04	Normal
H L H 76403	9m		0	++	+	3 7	68	15	0 92	Large lymphocytes 44%
Day	14m	6w	0	++	+	3 3	80	10 1	1 2	Lymphocytosis
						2 0	60	23	1 5	
H L H 68952	16m		0	++	+	4 4	90	7 6	1 02	Normal
Schuszik	21m		0	+	++	3 7	56	5 5	0 76	Normal
Hanau	21m	21m	0	+	++	3 5	60	14	0 86	Normal
Hofmann u Hausmann	2y		0	++	+	3 7	85	10 8	1 15	Lymphocytosis
Reuben and Peskin	20m	10m	+	+	++	3 4	65	9 2	0 95	Normal
Abt, I	2y		0	++	+	4 0	80	16	1 0	Normal
H L H 73713	2y	12m	0	++	+	2 7	68	8 3	1 26	Lymphocytosis
Bridgman and Robertson	2y	18m	+	+	+	2 4	50		1 04	

Warkany	3½y	3y	0	+	++	3 6	54	1 7	0 75	Thrombopenia, neutro penia	Splenectomy
Warkany	3½y	3y	0	+	++	3 6	54	1 7	0 75	Thrombopenia, neutro penia	Splenectomy
Debré et al	3½y	3±y	0	++	++	4 8	98	11 0	1 02	Normal	
Opitz	4y		0	++	++	3 7	80	12 4	1 08	Thrombopenia	
Halbertsma	6y		0	++	++	1 06	72	2 2	0 89	Neutropenia	
H L H 90241	6y		0	+	+	4 2	70	3 3	0 83	Thrombopenia	
		Few mos	+	++	+	2 3	60	17	1 30	Thrombopenia	
				++	+	2 1	52	19	1 24	Normal	
Debré et al	7y	6±v	0	++	++	3 3	70		1 06	Lymphocytosis	
Thoenes	7y	5y	0	++	0	3 4	50	10 7	0 73	Normal	
H L H 50550	8y	2+y	0	++	++	2 9	68	4 4	1 17	Neutropenia	
Reuben and Peshun	8y	8w	+	++	0	2 8	78	6 2	1 39	Neutropenia, thrombo- penia	
Opitz	8y		0	++	++	2 9	45	1 8	0 78		



TABLE 3

*Hepatomegaly without cirrhosis*

	AGE	LIVER	SPLEEN	BLOOD				
				Red blood cells	Haemoglobin	White blood cells	Color index	
Ellis and Hutchison	4m	+++	0	4 1	85	12 5	1 04	Hypertrophic steatosis
Debré and Semelaigne	9m	++++	±	2 5	75		1 50	Glycogen disease
Schall	14m	++++	0					Glycogen disease
Unshelm	19m	++++	0	3 3	80	13 6	No anaemia	Glycogen disease (?)
Solomon and Anderson	22m	++++	0	3 7	75	15	1 21	Lymphocytosis
				3 4	63	12	1 01	Lymphocytosis
Rauh and Zelson	26m	++++	0	3 9	70	16 6	0 93	Lymphocytosis
Kramer et al	9m	++	0	3 8	71	10 6	0 90	Lymphocytosis
Wilder	3y	++++	0	4 1	78	10 4	0 92	Lymphocytosis
Loeschke	3y	++++	0	4 2	75	25	0 95	Lymphocytosis
Exchaquet	4y	++++	0	2 0	40	10	1 00	Lymphocytosis
				3 1	58	35	0 92	Lymphocytosis
	4y	++++	0	3 2	78	7 4	1 24	Lymphocytosis, neutropenia
Schall	4y	++++	0				"No anaemia"	Glycogen disease
Comby	5y	++++	0			12 5	"Slight anaemia"	Glycogen disease
Anderson and Vickery	4y	++++	0			6 8	"Lymphocytosis"	(?)
Warner	5y	++++	0	4 9	80	0 82	Normal	(?)
v Creveld, '34	6y	++++	±			No anaemia	Lymphocytosis	Glycogen disease
Gottche	7y	++++	0	4 2	73	12	0 87	Normal
Biedermann u Herz	8y	++++	0		70	4-5		Glycogen disease (?)
	10y	++++	0		40			Glycogen disease

Schall	8y	+++++	0	{			No anaemia.			Normal	Glycogen disease (?)
				3	5	77	16	1	10		
Smith and O'Flynn v Creveld	6y	+++++	0	3	9	51	20	0	66	Slight lymphocytosis	Glycogen disease (?)
	10y	+++++	0	Slight anaemia			2	9		Neutropenia	
Worster Drought and I P Weber	10y	++	0	5	2	80	Once 11	0	73	Normal	Glycogen disease (?)
	9y	+++++	0	4	2	88	9	8	1	05	
Wagner and Parnas		+++++	0								

411, 647) Some anaemia may be present but no more than might be expected from the condition of the child From the work of Wolbach and others it is likely that the so-called cysts are no more than ducts dilated as a result of occlusion

## I DISEASES OF THE LIVER

1 *Cirrhosis of the liver* (table 2) As is well known anaemia of moderate severity is frequently encountered in cirrhosis of the liver. The anaemia is rarely severe, however, and haemoglobin values below fifty per cent appear to be uncommon The red cells are reduced to a greater extent than is usual in anaemias of infancy and childhood so that the color index tends to lie for the most part in the neighborhood of 1.00 Occasionally color indices above 1.20 are seen It is true that the presence of jaundice may give apparent haemoglobin values above the real ones, but the maximum error from this source does not exceed about ten per cent, and the jaundice present in these cases was rarely sufficient to introduce an appreciable error The white cells are usually increased in infancy and lymphocytosis is not infrequently encountered In somewhat older children up to seven or eight years of age lymphocytosis appears to be much less common, its place being taken by leucopenia and neutropenia In the cases above ten years of age blood changes of any sort were distinctly uncommon Platelets were frequently reduced in the intermediate age group but not in infancy Nucleated red cells were generally absent

2 *Hepatomegaly not associated with cirrhosis* (table 3) This group comprises the cases of "glycogen disease" and the possibly closely related "hypertrophic steatosis," described by Debre and first studied in any detail by Kramer, Grayzel, and Solomon In these cases anaemia is rarer than in cases of cirrhosis and in only one case was it at all severe The most outstanding finding is lymphocytosis with moderate increase in the white cells Leucopenia with neutropenia was found twice in older children

3 *Atresia or congenital absence of the bile ducts* (table 4) In this group, confined of course to infancy, anaemia is very moderate in degree when it occurs It is unfortunate that in the majority of reports the author has not bothered to include blood studies From the available cases we may observe a tendency to increasing anaemia

with increasing age. The color index was not above one in any case, and lymphocytosis occurred three times.

4 *Primary tumors of the liver* These are among the rarest malignant tumors that occur in infancy and are included not because of any importance as an etiological factor in the anaemia of infancy, but because in a discussion of the relation between liver disease and anaemia the type of anaemia occurring in association with malignancy

TABLE 4  
*Atresia of the bile ducts*

	AGE	HAEMORRHAGE	LIVER	SPLEEN	BLOOD				
					Red blood cells	Haemoglobin	White blood cells	Color index	
H L H 85803	3m	0	+++	±	4 1	76	13 60	0 93	Normal
H L H 33130	6w	0	+++	++	4 5	81	13 40	0 90	
H I H 61737	4m	+	++	++	3 6	60	23 70	0 83	Normal, thrombopenia
H I H 91067	4m	0	++	+	4 3	75	9 0	0 87	Normal
Kirschbaum	4m	0	±	±		50	11		Lymphocytosis
Hill	5m	+	+	±	4 9	77	13 0	0 79	Normal
H L H 48187	5m	0	++	+		45	10		Normal
H I H 46459	5½m	0	0	+	3 5	60	30 0	0 86	Lymphocytosis
Watkins and Wright	6m	0	+	-	3 7	70	10 20	0 95	Lymphocytosis
H L H 91067	7m	0	++	+	3 4	66	18 0	0 97	Normal
Dever	8m	0	++	+	3 2	70	18 1	0 09	Normal, thrombopenia
Watkins and Wright	1y	-	-	-	3 1	28	3 60	0 45	Neutropenia
H L H 91067	17m	0	++	++	2 0	32	5 40	0 80	Neutropenia, thrombopenia, reticulocytes 0

has some significance. As may be seen, anaemia occurs and may be severe (158, 211, 320, 651), but there seems to be a relation between duration and severity (233, 375, 470, 522, 746). The color index tends to be usually in the neighborhood of 1.00. Lymphocytosis was uncommon, and leucopenia did not occur. Normoblasts were present in one case.

The relation of the disease of the liver to anaemia is an almost untouched field of investigation. In the last few years interest is being

taken in this subject following the contribution of Wintrobe and Shumacker calling attention to the existence of a macrocytic anaemia in cases of widespread cirrhosis of the liver, and suggesting the possibility that in these cases there may be failure properly to store haemopoietic factor. Improvement that has been reported following liver therapy supports this hypothesis.

As may be seen from this compilation of cases of liver disease hyperchromic anaemia tends to occur with some frequency. In addition there is (1) a tendency to "hypoplasia" (neutropenia and thrombocytopenia, absence of nucleated red cells) confined almost wholly to cirrhosis, and to the ages between three and eight years, and (2) a tendency to lymphocytosis in infants with cirrhosis and in non-cirrhotic hepatomegaly.

The relation between the anaemia and disease of the liver is not a simple one. A certain amount of chronicity appears to be necessary for its development but there is no relationship between the extent of the process in the liver and the degree of anaemia. The mechanism of the anaemia is not clear and there are almost no observations bearing on this point. The neutropenia and thrombocytopenia which are interpreted as evidence of "hypoplasia" occur independently of the anaemia. Hyperchromic anaemia is more frequently present in association with a haemolytic than with a hypoplastic process, but no studies to test the presence of increased haemolysis have been carried out.

If the "hypoplasia" and the anaemia are not dependent on the extent of the lesion they must be associated in some way with the process which has brought the condition about. It need only be pointed out that the spleen is almost regularly involved in the cases with cirrhosis which makes up the group in which the "hypoplasia" is present. This fact brings these cases into relationship with those in which there is primarily an involvement of the spleen and particularly of the reticulo-endothelial tissue, to be discussed in the next section.

#### J DISEASES INVOLVING THE SPLEEN AND RETICULO-ENDOTHELIAL SYSTEM

1 *Gaucher's disease* (table 5) Gaucher's disease in infancy is more acute than it is in older children or adults, and is characterized in

many cases by cerebral symptoms—gradually developing spasticity, opisthotonos, internal strabismus, mental retrogression, eventually loss of all voluntary motor function and in some cases apparently complete amentia (153, 297, 508, 479, 597) The pathological process is often as widespread as that in Niemann-Pick's disease from which it is with difficulty to be distinguished (153, 268, 364, 367, 492, 508, 570) The bone marrow is involved at an early age, (179, 508) and the process can be widely distributed in the bones by the end of the first year (550), though characteristic changes in the roentgenogram have not been reported before the end of the third year of life (346, 550, 692) Pick (550) and others have suggested that bone marrow involvement is hastened by splenectomy, and Pick speaks of an osseous form of the disease in which the lesions in the bones are out of proportion to those elsewhere Such cases have, however, not yet been encountered in infancy

**Blood** In the cases thus far studied, there is little if any reduction in red cells or haemoglobin in cases occurring before the end of the first year of life From then on, however, relatively severe anaemia occurs with considerable regularity After the third year of life anaemia again tends to be less severe The anaemia is of a "hypoplastic" or aregenerative type with tendency to neutropenia or lymphocytosis, few if any immature red or white cells Thrombopenia has been commonly present after the second year of life, before that time the platelets have been mentioned so infrequently that a generalization is impossible The absence of haemorrhagic diathesis in infancy would seem to indicate that platelet reduction may not occur to the same extent as later While neutropenia is common enough in infancy a total reduction in white cells is only rarely encountered before the end of the second year Except in the case reported by Guglielmo, Gaucher cells have not been seen in the peripheral blood

The changes in the blood have been attributed to involvement of bone marrow There are certain facts, however, that cast doubt on this The severity of the anaemia bears no constant relation to the extent of the marrow involvement In osteosclerosis and marble bones we see the picture that results from marrow replacement in its pure form, and the characteristic blood picture of Gaucher's disease

TABLE 5  
*Gaucher's disease*

	AGE	DURATION	BLOOD				HAEMORRHAGIC TENDENCY	LIVER	SPLEEN	BONES (X-RAY)	BONE MARROW (AUTOPSY)	
			Red blood cells	Haemoglobin	White cells	Neutrophils						
Oberling and Worringer	1m		4 3	75	5 7	24		+	+	+	+	
Dienst	3m	3+w	3 8	50	8 8	22		+	+	+	+	
Reber	7m		3 5	56	9 6	40		+	+	+	+	
Stransky	6m		2 4	58			-	+	+	+	+	
Oberling and Worringer	10m	5m	5 2	65	11 3		0	+	+	+	+	
Oberling and Worringer	11m	8m	4 4	54	6 3	43	0	+	+	+	+	
Nagao	11m	10m	5 0	50			0	+	+	+	+	
Donovan	11m	3+m	4 0	60	7	50	0	+	+	0	+	
Rusca	11m	4m	3 1	40	12 7	40	0	+	+	+	+	
Reiss and Kato	15m	5m	2 0	35	10 6	53	0	+	+	+	+	
Guglielmo	16m	1m	3 1	65	8 2	12	0	+	±	+	+	
Hoffman and Makler	17m	2m	2 6	24	3 8	35	0	+	+	0	+	
Frick u. Friederich	18m		4 0	39	16 8	68	0	+	+	0	+	
Graham and Blacklock	18m	7m	2 1	20	8 6	31	-	+	+	0	±	
Schuster	22m	3+w	1 07	28	4 0	56	±	±	+	+	+	
Kretsch u. Paschun	2y	18m	1 8	24	3 7	65	-	+	+	+	+	

Author	Age	Sex	Duration of illness	Platelets	Leucocytes	Neutrophils	Monocytes	Eosinophils	Lymphocytes	Splenectomy
De Lange	2y	6m	3 1	46	7	41				
	4y	2y	4 3	57	4 2	51				
Ullrich	2½y	1y	3 7	55	11	42				
	5y	3y	2 0	46	4 7	31				
Meyers	2½y	3y	3 5	70	16	25				
	3y	2½y	1 3	19	2 2	44				
af Klercker	3y		3 4	35	2 5	49				
	3½y		4 3	76	15					
Fahr u Stamm	3y	1y	2 1	30	5 8					
	3y	2w later		18						
Reiss and Kato	3y	1y	4 7	78	8 0	63				
	3y	2y	2 3	25	6 4	40				
Reiss and Kato	3y	2½y	4 0	70	1 1	65				
	3y	3½y	3 0	80	24	56				
Reiss and Kato	3y	1y	3 8	70	6 9	73				
	6y	4y	3 1	68	12 5	47				
Abrahams	4½		5 0	60	4 4					
	5y		4 1	62	5 5					
de Lange	5y		3 8	75	7 9					
	6y		2 0	30	5+ 40-50					
Capper et al	8 mos later		No	naemia						



bears no resemblance to it<sup>3</sup> While these facts do not exclude bone marrow involvement as a factor in the blood picture, Ullrich's observation that the anaemia became less marked after splenectomy while the bone lesions became more intense indicates that the process in the spleen itself is probably a factor in the development of "hypoplasia"

There is no clinical evidence for increased blood destruction The deposition of iron in the spleen cannot be accepted as such evidence, for it may be due to increased tendency to retain iron rather than excrete it Studies of stool urobilin excretion are needed to settle this point as well as determination of iron balance or other methods for testing iron retention

2 *Niemann-Pick disease* In Niemann-Pick's disease the red cells and haemoglobin are reduced to a very moderate degree if at all, the red cells seldom going below three and a half million, and the haemoglobin below about fifty to fifty-five per cent Leucopenia occurs occasionally in the second year of life (361, 611) Relative neutropenia is fairly common, but in absolute numbers the neutrophils are usually not reduced The lymphocytes are usually increased in absolute numbers and occasionally there is considerable lymphocytosis or monocytosis (41, 188, 351, 559, 636) Pick mentions especially the presence of vacuolated cells, which were noted in only three cases outside of his own (41, 188, 712) It must be remembered that the majority of authors have paid little or no attention to the blood and have merely reported the routine blood counts or none at all *Platelets* are only slightly if at all reduced, being below 100,000 only once Haemorrhagic tendency are present in no case

The bone marrow was regularly involved in the pathological process, but only rarely to any considerable extent, and never sufficiently to interfere with marrow activity Though the majority of reports mention a yellowish color to the skin, jaundice has not been present in any case

Because of the insignificance of the blood changes the table containing the blood findings in Niemann-Pick disease has been omitted

<sup>3</sup> An exception to this statement is found in a case of Lesné, Clement and Guilan in which there was fairly severe anaemia with increase in reticulocytes and the presence of erythroblasts and myelocytes

The foregoing account has been based on the following articles Abt and Bloom, Berman, Baty, Bloom, Corcan, Oberling and Dienst, Fisher, Hamburger, Knox and Ramsey, Knox, Wahl, and Schmeisser, Jenny, Kramer, Poncher, Schiff, Schmitz and Thoenes, Was-cowitz, Smetana

3 *Xanthomatosis* This term, introduced by Rowland, is used to cover a rather miscellaneous group of cases characterized by proliferation of cells of "reticulo endothelial" origin containing cholesterol and other lipid material The outstanding characteristic of this group is the tendency to involve bones, particularly the bones of the skull giving rise to the now well known Hand-Schuller-Christian syndrome with exophthalmos, diabetes insipidus, and not infrequently delay in growth The flat bones are most often involved, the long bones rarely, except the femora, and the process is usually fairly sharply demarcated from the surrounding bone, giving rise to well defined areas of destruction Outside of these areas the bone marrow is usually little involved

In these cases, in which the processes are circumscribed (table 6) even though their distribution may be wide, anaemia is usually not present or is mild, and there is nothing in the blood picture to attract attention In only three cases among those in the table was there severe anaemia, though it might have been found in the other fatal cases had the blood been studied more closely There is little to lead to any idea concerning the nature of the process responsible for the anaemia In the two cases sufficiently studied, it was striking that the anaemia developed with great rapidity in the last few weeks of life

In table 7 I have collected those cases in which the bone involvement was much more widespread It is noticeable that the whole process appears to be more widely distributed throughout the body, for the liver and spleen are regularly enlarged, that the majority of the cases occur in infancy, and that the Schuller-Christian syndrome is not present—only one case showed diabetes insipidus at the onset two years before the fatal ending There is no reason to separate this group from the other except for convenience in classifying separately a more widely diffused and rapidly fatal form

The blood picture in these cases is striking and suggests that of

TABLE 6  
*Xanthomatosi—circumscribed process*

	AGE	DURATION	BLOOD					HAEMORRHAGE	LIVER	SPLEEN	BONE (X-RAY)	BONE MARROW (AUTOPSY)
			Red blood cells	Haemoglobin	White blood cells	Neutrophils	Erythro-blasts					
Morison	8m	1m		68	16 2		0	0	0	0	Scapula, skull	—
Morison	2y							0	0	0	Ihum (later), skull, vertebra, pelvis, femur	—
Natali	2y	4w						0	0	0	Skull, ihum, vertebra, femur	—
		2y						0	+	+		
		later										
Rowland	2½y	6m	3 8	68	9 8	71	0	0	0	0	Skull, ihum	—
		2y	5 6		13 5	67	0		0	0	Skull	+
		1y							—	—		+
Grady and Stewart	3y	6m	3 8	60	12 6	70±	0		—	—		—
Sosman	2½y	7m	4 4	70	12 6	71			—	—	Skull, ihum, scapula	—
Savage	3y	5m	4 2	72	10 9	49			—	—	Skull	—
Krauss u Barth	3y	6m	3 5	45	14	71			+	+		—
		1y		90			0	0	+	+	Skull, ihum, vertebra, femur	—
Heard, Schumacher and Gordon	3y							0	0	0	Flat bones	+
Attig	3y	1y	4 7	70	5 0	49	0	+	+	+		
		2w	0 9	20	6 0	44	0	+	—	—		
		later							0	0		
Lesné, Lièvre et Boquien	3y	1y	3 2		16	79	0	0	0	0		—

Schneider	3y	2 7 55 2 6 35 1 9 25	2 7 55 2 6 35 1 9 25	57 40 41		0	0	0	Skull, pelvis, femora	1
Anspach	5y	4 6	9 2	6 4		0	0	0	Skull, vertebra	1
Mettel	5y	3 4 85	6 8	80	0	0	0	0	Skull, alium, femur	1
Sosman	5y	4 5 50	6 4	67	0	0	0	0	Skull, femur pelvis	1
Ighenti	4y	4 8 92	95	63		+	+	+	Skull, femur pelvis	0
		1+y				Petech				
Miyaji	4y	4 3 73	16 4	55		0	+	+	Skull, humerus	1
Rowland	5y	4 6 65	17 6	73		0	+	+	Skull	+

Monocytes 17%  
"Increasing anaemia"

Monocytes 20%

TABLE 7  
*Xanthomatosis—generalized form*

	AGE	DURATION	BLOOD						HAEMORRHAGE	LIVER	SPLEEN	BONES (X-RAY)	BONE MARROW (AUTOPSY)
			Red blood cells	Haemoglobin	White blood cells	Neutrophils	Erythroblasts						
Rietschel Lichty	12m	3w	4 3	65	26 7	55	+	Platelets 79,000	Petech	+	+	+	+
	21m	6m	0 9	15	7	47	+	Thrombopenia	+	+	+	+	+
Merritt and Pauge Gerstel	2y	1y	3 5	58	2 6	55	—	Platelets 22,000	+	+	+	+	+
	3y	2y	2 2	35	5 +	40 ±	—		Petech	+	0	+	—
	2y	4w	3 4	40	9 2	52	—		+	+	+	+	+
	2y	6m	1 5	36	4 5	77	+		+	+	+	Skull	+
Schultz, Werbter and Puhl	2y	5m	1 2	26	6 9	77	+	Platelets 46,000, megaloblasts	Petech	+	+	+	+
		4w later	0 98	14	17 8	56	+		+	+	+	+	+
Berkheiser	3y	1y	3 5	44	7		—	Platelets 22,000, megaloblasts	—	—	—	+	+
	2y	2y	3 5	29	11 9	50	—				0	+	+
Herzenberg	5y	6w later	0 74	7	11	30	+		Petech	+	+	—	+

bone marrow replacement, rapidly developing anaemia, reduction in platelets, tendency to haemorrhagic diathesis, and increase in erythroblasts, the same picture that is encountered in osteosclerosis

4 *Hodgkin's disease* The influence of Hodgkin's disease on the blood picture varies with the stage of the disease, the severity and the extent of the pathological process, especially its presence in the bone marrow. In the early stages and during remissions the blood picture is essentially normal. As long as the disease progresses slowly, there is little if any anaemia, until it has reached an advanced stage when anaemia may be severe. Table 8 contains the cases reported in children up to five years of age. This table is not representative since in the majority of instances the reporting of a single case means that there was something unusual about it, and we must turn to such articles as those of Smith and Corbeille, who have reported large numbers more or less statistically, for our knowledge of the average case (124, 347, 491, 638). There is little that is characteristic. In the rapidly progressive case the anaemia tends to become severe and is usually of a hypoplastic variety. While leucocytosis often with relative lymphopenia is the rule, leukopenia frequently is present in those cases that develop anaemia. The relative and often absolute reduction in lymphocytes is stressed by all writers on the subject and is linked with the severity of the disease, for a fall in lymphocytes is generally regarded as a bad prognostic sign. The development of leukopenia and thrombopenia with tendency to haemorrhage, in the cases with severe anaemia, indicates involvement of the bone marrow (31, 183, 95, 499), as does also the case of Wollstein and McLean with erythroblastosis. It is of course possible that a terminal aplastic blood picture may be the result of too vigorous treatment with X-ray or radium. The case of Nicolaeff and Zimble might belong here, as well as a case cited by Corbeille.

Involvement of bone and bone marrow in Hodgkin's disease has recently come in for considerable attention (127, 370, 483, 564). Uehlinger has recently reviewed the subject thoroughly and finds that in those cases with no bone involvement or merely a localized circumscribed process in the bone there is little tendency to anaemia, and in those cases, much more rare, in which there is widespread dissemination of the process, anaemia and leukopenia may develop rapidly

TABLE 8  
*Hodgkin's disease*

	AGE	DURATION	BLOOD					HAEMORRHAGE	LIVER	SPLEEN	BONE MARROW (AUTOPSY)	
			Red blood cells	Haemoglobin	White blood cells	Neutrophils	Erythro- blasts					
Pinelli Wollstein and McLean	4m	2m	2 6	45	6 5	76	±	Lymphopenia	±	-	-	Cf "Reticuloendo- theliosis" Outcome? Died Acute course Well after 6 yrs Died Died Acute course, cf "Reticuloendo- theliosis"
	8m	6m	2 6	35	5 6	68		Platelets 88,000	++	++	Not men- tioned	
	4½m	1m	2 8	55	12 5	64	+		++	++		
Cattel	5½m	3m	3 9	70	14 4			Lymphocytosis	-	-	-	Died
	22m	20m	4 5	75	17	26			0	0	Not men- tioned	
	8m	3m	3 9	54	5 8	61	-	Lymphopenia, mono- cyte in- crease	0	+	-	
Herlitz and Wallgren	9m	9m	2 6	33	5 6	90	-		0	-	-	Acute course
	15m	10m	2 8	36	3 6		-	Reticulocyte in- crease	-	-	-	
	18m				8 7	46	-		-	-	-	
Feer	3y	9m	3 9	65	7 7	20			-	-	-	Died
		2y	4 1	80	15	56	-		-	-	-	
	3y	2m later	2 5	60	9 4	74	-	Lymphopenia	+	+	-	
Huhn	3y	2y	3 0	50	8 0				+	+	-	Died
			1 8	32	7 2				+	+	-	
	3y	6m	4 7		14	86			+	+	-	
Huhn Baar	4y	6w	0 9	10	2 4	58		Thrombopenia	+	+	+	Died
								Petech	+	+	+	





The rapidity with which anaemia develops is a relative matter. From the cases in the table we see anaemia developing over a period of eight to ten weeks or longer, but apparently never with the speed that we encounter in the haemolytic group. Although there is usually little that is characteristic about the anaemia of Hodgkin's disease except when signs of hypoplasia supervene, occasionally there may be clear evidence of increased blood destruction. The increase in reticulocytes in Levy's case suggests this. Also one of Huhn's cases with a pernicious picture suggests it. Davidson has reported cases in adults in which the anaemia is clearly haemolytic. More attention to the nature of the anaemia in Hodgkin's disease is needed.

There is perhaps no better illustration than in many reports of Hodgkin's disease of a tendency which is actually present throughout all of medicine when it comes to a study of the blood. Diagnosis is too often considered in terms of the giving of a name not in terms of the understanding of a process. Again and again we see in these tables only one report on the blood and one is left wondering what happened as the disease progressed, or the bones became involved. Such omissions can mean only that either the person who reported the case or the one who studied it was not very much concerned with what was going on and what the study of the blood could tell him. Those who report the picture of Hodgkin's disease statistically seldom pay attention to the blood because it is of little importance in diagnosis. Others report important blood changes casually and do not mention the bone marrow in their report. These are not isolated instances. It is not so much that the blood findings are not reported, if they are unimportant, but that the reader of the article is not permitted to judge for himself and the blood is considered unimportant for the wrong reasons. A "normal" blood picture may be unimportant from one point of view, but if the autopsy showed widespread destruction of bone marrow, the "normality" of that blood picture becomes of the utmost importance. Diagnosis is not the giving of a name, it is the understanding of what is going on, how it started and why, the blood is important as a means of assisting our understanding, not merely as a help in classification.

5 *Reticulo-endotheliosis* This is a term applied to a group of cases in which there is found at autopsy a widespread proliferation of a type

of cell which is interpreted as arising from the reticulo endothelial tissue. It is a useful term for grouping together a number of cases as having certain histological features in common, but it is not to be looked on as a disease entity.

Several attempts have been made to classify the conditions in which there occurs reticulo endothelial proliferation. They may be divided into four groups according to Uehlinger's scheme and nomenclature.

1 Storage reticulosis—Gaucher's disease, Niemann-Pick disease, xanthomatosis, and cases with storage of lipid material following lipemia as in diabetes.

2 Infections—reactive

(a) Specific etiology (as in typhoid, malignant endocarditis, tuberculosis)

(b) Etiology non-specific, but possibly infectious in origin

3 Hyperplastic group (Cases without any characteristics pointing to any etiological factor)

4 Dysplastic group (Malignant tumors—leukemia)

This classification cannot be regarded as in its finished state. The second and third divisions are too ill defined to be considered permanent. Hodgkin's disease belongs somewhere among these conditions, probably under 2 a or 4.

The cases that have been collected in table 9 occurring in infancy and early childhood form a special group that clinically and pathologically have much in common, and form the majority of the cases constituting group 2 b. The course is that of a subacute sepsis with which the entire clinical picture is compatible. The spleen, liver and lymph glands are enlarged, there is an intermittent fever, and there may be a moderate degree of anaemia. The bone marrow is involved probably in all cases, but the X-ray examination does not always demonstrate it. The changes in the blood are not very constant or characteristic, being those of a severe infection or sepsis—some tendency to neutropenia and thrombocytopenia, occasionally immature forms. In one case the picture was that of aplasia both clinically and pathologically but in the others there appeared to be no relation between the blood picture and marrow involvement. Nearly all the cases have shown a haemorrhagic tendency at some time in the

TABLE 9  
*Reticuloendotheliosis*

	AGE	DURATION	BLOOD						HAEMORRHAGE	LIVER	SPLEEN	BONES (X-RAY)	BONE MARROW (AUTOPSY)	
			Red blood cells	Haemoglobin	White blood cells	Neutrophils	Erythro- blasts							
Guzzetti	3m	2w	3 0	70	15 3	45	±	Megaloblasts	+ Petech nose	+	++	Skull, femur, humerus	±	
Letterer	6m	10w	5 6	65	26	65	-	Platelets normal	+ Petech	+	++		±	
Roussy and Oberling	8m	8d	4 1	36	10 0	12	-		+ Petech	+	++		++	
Podvinec and Terplan	12m	9d	3 2	65	10 8	43	-	Platelets 140,000	+ Petech	++	++		±	
v Creveld	4½m	2w 9w	4 6 4 7	58 57	10 2 8 2	52 37	0 0		0	+	+	Skull, hu- merus, rib, femur	+	
Klostermeyer Siwe	13m 16m	7w 3m	2 1 2 4	31 40	2 0 12 5	0 62	0 ±	Immat lymphos Platelets 1,500,000	0 +	++	+++	Skull Fibula	+	Leukaemia?
Uher	21m	Few days	3 2 4 2	80 88	11 9 7	74 76	±	Platelets 47,000, myelocytes 7%, shift to left	+ Petech	+	+		±	
Parsons and Hawksley, Gittins	21m	10d	1 4	26	0 95	8	0	Platelets 21,000	+ Purpura	0	+		+	Bone marrow aplastic
Gittins	23m 3½y		2 5 3 7	37 75	11 3 4 0	44 50	± 0	Platelets 10,000 Platelets 80,000	+ 0	0 ++	0 ++		+	
Foot and Olcott	2y	1y							Petech					Splenectomy, Hodgkins disease?
Abt and Denenholz	2y	6w 4m	3 5 1 2	60 30	4 9 2 8	63 46	-	Platelets 300,000 Platelets 342,000	+ Petech		++	Pelvis, femur Skull	++	
Krahn	5y	6m	1 06	13	3 0	13	0	Platelets 99,000	+ Petech	++	0			Bone marrow aplastic

course The condition may be suspected on clinical grounds, but diagnosis at the present time rests on the findings at autopsy

There is nothing in the reported cases that indicates that we are dealing with a disease entity Rietschel points out their similarity to cases of generalized xanthomatosis On the other hand in many ways they resemble Hodgkin's disease, differing principally in the wide dissemination of the process and the acuteness of the course The pathological picture is identical with that of those portions of the xanthomatous process in which lipoid material has not been deposited, and there may be in Hodgkin's disease sections without the typical Dorothy Reed cells in which differentiation from reticulo endotheliosis is impossible The case described by Schultz, Wermbter and Puhl was reported as a "granulomatous system-disease of the haemopoietic apparatus" It is placed among the xanthomatoses by Chiari and by Rowland, it is called Hodgkin's disease by Baar, it is considered a malignant tumor by Epstein Foot and Olcott noted the resemblance of the changes in the spleen in their case to those of Hodgkin's disease The description of certain cases of Hodgkin's "sarcoma" strongly suggests that they may belong in the group we are discussing, and the case of Wollstein and McLean of Hodgkin's disease of the thymus, with a slightly different interpretation might easily fit the picture of reticulo-endotheliosis Dameshek places Krumbhaar's case of Hodgkin's disease of the bone marrow in this group, and considers the possibility that the two conditions may be different manifestations of the same disease

6 *Splenic vein thrombosis* This condition has lately come into prominence largely replacing Banti's disease as an explanation of splenomegaly with haematemesis, at least in children The diagnosis as used at the present time does not depend on the demonstration of the thrombosis but on changes in the spleen that are explicable only on the basis of venous stasis The cause of the stasis is demonstrated in a minority of the cases and it is unusual to learn anything of the events leading up to the anatomical changes Clinically these cases are characterized by the following (1) Haematemesis, usually the symptom to bring the patient under observation, and often mistaken for gastric ulcer (2) Fluctuations in the size of the spleen—enlargement between haemorrhages with marked reduction immediately

following one While these characteristic fluctuations are diagnostic, they are not always present (3) Occasionally ascites and intestinal haemorrhage usually attributed to mesenteric thrombosis or involvement of the portal vein (4) Rarely cirrhosis of the liver

The examination of the blood may show characteristic changes There is of course anaemia as a result of the loss of blood, but the red cells and haemoglobin often do not rise as rapidly as usual after haemorrhage The white cells and platelets are frequently found reduced both after haemorrhage and in quiescent periods (137, 239, 276, 516, 610, 704) Nucleated red cells are rare These changes indicate the presence of "hypoplasia" and are no different from those of the so-called "splenic anaemia," a most voluminous pigeon-hole too often containing anything with a splenomegaly and anaemia that cannot be placed anywhere else Opitz emphasizes the blood changes as characteristic, while Smith and Farber did not find them in their cases and feel that they have no significance As we have seen, the same "hypoplastic" picture is encountered in other conditions with splenomegaly, such as Gaucher's disease, cirrhosis of the liver, Hodgkin's disease, and "reticulo-endotheliosis," and often disappears after splenectomy It is hard to escape the possibility that a proper valuation of the blood changes might lead to a better understanding of the condition

The syndrome of splenic vein thrombosis has usually occurred beyond the age of three years but it has been reported in infancy, and in many older children a history of splenomegaly goes back to infancy even though the first haematemesis did not occur until later (137, 239, 641, 667, 704, 735)

#### K INVOLVEMENT OF BONES

*Osteosclerosis* (table 10) Clinically this condition appears to be of two types (M B Schmidt) (1) a "primary" type, frequently having a familial incidence, often beginning in infancy or childhood, and going under the name of Albers-Schonberg's disease, *osteosclerosis fragilis generalisata*, *marblebones*, *osteopetrosis*, and (2) a "secondary" type associated with various diseases of haemopoietic system, especially leukemia A distinction between these two types is not always clear The cases that have been reported in infancy and early childhood

TABLE 10  
*Osteosclerosis*

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	AGE	BLOOD					HAEMORRAGE	LIVER	SPLEEN	BONE INVOLVEMENT	Simulated congenital haemolytic jaundice, bone x ray typical at 2y
		Red blood cells	Haemoglobin	White blood cells	Neutrophils	Erythroblasts					
Frank	2w	3 8	80	25		+	Platelets 70,000	-	-	?	
	5w										
Goodall	10w	1 1	22	75	26	+++	Myelocytes 16%, myeloblasts +	+	-	+++	
Guassardo	3m	3 6	58	40	18	++	Monocytes 24%, myelocytes and myeloblasts	-	-	+++	
McCune and Bradley	3m	3 7	70	8 2	73	-	Myelocytes 13%, platelets 36,000	0	+++	+++	
	4m	1 5	48	60	28	++			+++	+++	
	8m	0 9	20	17	58	++	Monocytes 19%, platelets 50,000	+	+++	+++	
	4m	3 3	48	62	25	+++			+++	+++	
Kudrawtzeva Pease et al	8m	3 8	71	8 3	46	0	"Changes in red cells as marked as in pernicious anaemia"	-	-	++	Early changes
	8m								++	++	
Robertson	10m	3 5	60	7	23	+	Monocytes 15%, myelocytes 7%, myeloblasts +	±	+++	+++	
Windholz	11m	4 3	48	5		-	"Normal"	0	±	+	Early changes
Hässler and Krauspe	12m	2 1	28	60	34	+++	Immature white cells, megakaryoblasts	+	+++	+++	
Karshner	11m	3 6	70	18	40	-	"Myeloblasts"	0	±	+++	+++
Oesterlin	2y	2 1	33	11	25	+		+	+	+++	+++
Kraus and Walter	3y	1 3	20			+			±	+++	+++
		2 7	33	13		+	Myelocytes 13%			+++	+++
Karshner Kudrawtzeva	3y	3 0	30	6 7	30	-		-	++	++	Early changes
	4y	3 7	68	8		45		-	++	+	

summarized in the table consist entirely of the primary type. As far as can be judged from the available information the blood changes depend largely on the extent of the involvement of the marrow in the sclerotic process, but the disease may show considerable advance before any change in blood picture takes place. In the cases with anaemia the outstanding features are (1) tendency to erythroblastosis, (2) tendency to leucocytosis sometimes extreme, (3) frequent preponderance of mononuclear elements—lymphocytes and monocytes, (4) tendency to immature forms among the myeloid elements particularly myelocytes though myeloblasts are also sometimes present, (5) tendency to reduction in platelets. Terminally there may be increasing evidence of hypoplasia with purpuric manifestations and haemorrhage. There is usually splenomegaly and often hepatomegaly, the spleen and liver being the seat of extramedullary blood formation, which has also been reported in the kidneys in young infants. Icterus is rarely present. In some of the early cases the condition was confused with leukemia and reported as such.

The blood changes have been ascribed to encroachment by the osteosclerotic process on the marrow spaces but autopsy has usually shown that the marrow is fibrous and that normal marrow tissue has almost completely disappeared in advance of the osteosclerotic process.

The secondary type has been described only rarely in childhood. Hassler and Krauspe reported a case in a two year old child with leukemia. In this case a biopsy showed only the osteosclerosis, autopsy revealing the true nature of the process. Frank's case is of interest, for it is possible that the osteosclerosis may have developed secondary to congenital haemolytic jaundice. The occurrence of osteosclerotic changes in sickle cell anaemia (484) renders this possibility plausible.

Apart from osteosclerosis the relation of processes involving bone or marrow to anaemia is not at all clear. In the case of *tumor metastases*, rare in infancy, changes in the blood depend quite as much on the type of tumor as on the extent of the marrow involvement which is rarely sufficient to produce a picture of bone marrow replacement. *Primary tumors* of the bone rarely cause anaemia until the terminal cachectic stage, except for those arising from the cells of the bone marrow. This subject has been discussed under "Tumors."

The group of conditions associated with splenomegaly and widespread involvement of the reticuloendothelial tissue in most cases are associated with lesions in the bones *Gaucher's disease*, *Xanthomatosis*, *Hodgkin's disease*, "*Reticulo-endotheliosis*" especially. It is rare, however, that the blood changes have been shown to be dependent on direct marrow involvement, except possibly in *Xanthomatosis*.

In *Leukemia* the marrow is regularly involved and marrow replacement probably plays a large part in the development of anaemia. Involvement of the bone in leukaemia can be recognized during life by changes in the roentgenograms which have only recently received adequate attention (128, 323, 325, 561, 645, 677).

The bone changes characteristic of the hemolytic-erythroblastic group of anaemias especially Mediterranean anaemia and sickle cell anaemia have usually been considered to be a result of the marrow hyperplasia.

In rickets and scurvy, as already stated, there is little reason to believe that the associated anaemia is due to direct involvement of the marrow in the same process that affects the bones. In congenital syphilis on the other hand there may be a more direct relationship between bone involvement and anaemia though the usual presence of other possible factors renders such a statement difficult to prove.

#### L. LEUKAEMIA

It is hardly necessary to do more than touch on leukaemia since the anaemia is only incidental to the much more serious condition and leukaemia is thoroughly described in every text-book. It need only be pointed out that leukaemia is not uncommon in infancy, at which time it is invariably acute and often appears in an aleukaemic form. The term "*aleukaemic*" has two meanings (1) leukaemia with a normal blood picture, (2) leukaemia with marked reduction in white cells but in which the cells are evidently abnormal. The first is extremely rare though apparently it does occur. The second occurs frequently though in many cases the abnormality of the cells may not be great enough to assure the diagnosis on a single examination. The type of anaemia in the acute case is aplastic with low reticulocyte count and absence of nucleated red cells. The platelets are greatly reduced or absent. During remissions the blood may approach normal but it is



rare that the blood picture does not contain elements that permit the diagnosis or at least the strong suspicion of leukaemia. The subject is mentioned for completeness but it is rare in infancy that the case presents itself as an obscure anaemia, for which one must find the explanation. It is rather the leukaemic state that must be differentiated, and the anaemia is a by-product that does not assist much in the diagnosis.

From the point of view of pathogenesis of the anaemia these cases are interesting. Evidently the anaemia is dependent on replacement of haemopoietic tissue by the leukaemic process. In other cases, however, of bone marrow replacement there is a tendency to erythroblastosis as seen in osteosclerosis, xanthomatosis, tumor metastases, and also in the chronic myeloid leukaemia. In acute leukaemia on the other hand, nucleated red cells are not seen and the blood picture is completely aplastic. It seems not unlikely that the leukaemic process causes blood forming tissue to differentiate in an abnormal direction to the almost complete exclusion of normal haematopoiesis, even in those places where extramedullary blood formation might take place, so that there is little possibility of new development of blood forming tissue to supply the needs of the body. It is interesting that in remissions normal blood formation increases as if the leukaemic process had paused and allowed the cells to develop in a normal direction temporarily.

#### CLINICAL TYPES OF ANAEMIA

In this work I have attempted to classify the anaemias along the line of Pathogenesis. For this purpose they have been grouped under three heads. (1) Those characterized by increased haemopoietic activity, the "haemolytic-erythroblastic" group, (2) Those characterized by decreased haemopoietic activity, the "hypoplastic-aplastic" group, and (3) those due to deficient haemoglobin formation, the "hypochromic" group. There is no completely satisfactory system of classification for a subject of such extreme complexity, and there are many drawbacks to the one used here, not the least being the fact that we must infer the process from changes in the peripheral blood.

Another objection is that in many cases more than one process is effective. Thus in the haemolytic-erythroblastic group, signs of hypoplasia may be present as well as deficient haemoglobin formation, and in the hypoplastic group increased hemolysis may occur, etc. On the other hand, similar objections can be brought against any system of classification. (The prevailing system in adult medicine based on cell size or mean corpuscular volume is meaningless in infancy.) The system based on pathogenesis has the advantage of being simple and logical, avoiding the confusion that comes from the multiplicity of names, and the meaningless division into "primary" and "secondary."

#### A THE HAEMOLYTIC-ERYTHROBLASTIC GROUP

The cases belonging to this group are characterized by (1) Great reduction of red cells as well as haemoglobin. (2) Increased blood destruction, (3) Changes in the blood indicating increased regeneration, (4) Often the presence in the blood stream of immature cells, (5) In some cases, especially more severe ones, evidence of "hypoplastic" reaction.

(1) The color index tends to be in the neighborhood of 1 or above, though sometimes a low index may be encountered, and in certain groups (Mediterranean anaemia) a low index is the rule. Anisocytosis is a constant feature with mean diameter about normal or somewhat increased, except in Congenital Haemolytic Jaundice. Mean corpuscular volume is usually above the normal. Poikilocytes are often present.

(2) Increased blood destruction. Jaundice may be absent, especially in infants, but there is usually a peculiar subicteric tint to the skin often described as "muddy." The Van den Bergh reading may not be significantly raised. The most useful procedure for determining the presence and severity of the haemolytic process is the estimation of the daily urobilin excretion in the stools. Cooley and Lee have recently emphasized the presence of fragmentation of red cells in fresh blood films.

(3) The reticulocytes are with few exceptions increased in this group of anaemias. It must be remembered, however, that they are also increased to a slight extent in other forms of anaemia in which in-

minor rôle. The upper limit in the number of white cells that any figure above this is of course dependent on the degree of stimulation from medicinal agents. The white cells are often increased in the absence of an infection, and in infants may reach high values in some instances above 100,000. When white cells are often present, sometimes in enormous numbers, the presence indicates injury to the haemopoietic process, but does not necessarily mean a bad prognosis. Megaloblasts may be found. The tendency to immaturity often spreads to the white cells both of the myeloid and of the lymphocytic series. While infections, which are so often present in these cases, probably play an important part in these leukocytic reactions, there are other little understood factors. The cases in which the immaturity factor is present are the ones usually classed under the von Jaksch syndrome.

(5) In a fairly large proportion there is evidence of a tendency to "hypoplasia". In many lymphocytosis occurs in place of the expected polymorphonuclear response. Platelets are frequently diminished even when the other elements give no evidence of "hypoplasia". In some there may also be neutropenia and in a very small group the erythropoietic system may be involved in the "hypoplasia" with reduction in the number of erythrocytes and nucleated forms (108, 225). The cases in which it are often classified under "per-

cases, however, nucleated red cells appear as the result of a crisis, while absent at other times. This is the first step in a series that leads up to the "erythroblastic anaemia" in which hemolysis may play a relatively minor rôle. Whether there is such a thing as a pure erythroblastic anaemia with no increase in blood destruction is at present unknown. There are, however, plenty of cases in which there is apparently no evidence of any increase in blood destruction. We must wait for quantitative determinations of urobilin excretion in the stools before we can obtain an answer to this question.

In addition to the two pathological processes of increased blood destruction and failure of maturation there is the third factor of "hypoplasia"—reduction of platelets, neutropenia, in rare cases signs of diminished red cell regeneration. Occasionally, we may encounter a case in which there is progression toward "hypoplasia" as if the injury to the haemopoietic function had become more severe, so that not only was maturation interfered with but the cells were not even being formed (395, 740). This would suggest that erythroblastosis or failure of maturation is an intermediate step in the development of aplasia. There is, however, little evidence for such an implication, although it may remain a possibility in an occasional case.

"Exhaustion of the bone-marrow" is another conception that has had popularity although there is no proof that it ever occurs. Such hypotheses that attempt to explain the relation of hypoplasia to the picture may be necessary as a basis for investigation, but they cannot, at present, be accepted as a solution of the problem however plausible they may appear on the surface.

*Classification of the haemolytic-erythroblastic group*

- 1 Dependent primarily on constitutional factors
- 2 Chronic cases dependent primarily on extrinsic factors
- 3 Acute haemolytic anaemia

This classification is probably over-simplified but it is designed merely to aid the discussion of the subject in this review. It is not so easy in practice to determine what factor is primarily at fault, and it is a common experience in this group to have to shift doubtful cases from one category to another as new information concerning the patient comes to light, or as knowledge is increased.

### *1 Constitutional types of haemolytic-erythroblastic anaemia<sup>4</sup>*

There are certain characteristics that are more or less common to the "constitutional" types and can best be discussed in a general way

*1 First appearance* These cases usually manifest themselves in early life but only rarely in early infancy. Often the disease makes its first appearance quite abruptly in relation to some rather mild infection. This type of abrupt onset is to be seen particularly in sickle-cell anaemia, but also occurs in congenital haemolytic jaundice (57, 145, 488). In Mediterranean anaemia this type of onset does not occur. The tendency to begin in early infancy is greatest in Mediterranean anaemia, it is much less common in congenital haemolytic jaundice and sickle cell anaemia.

*2 Latent forms* Both sickle cell anaemia and congenital haemolytic jaundice exist in a latent form in which the characteristic peculiarities of the red cells are present without increased haemolysis or haemolytic anaemia. In Mediterranean anaemia such latent forms have not been shown to exist, though the familial tendency suggests that there may be a latent form if we had "wit" enough to learn to recognize it.

*3 Crises* These are characteristic of congenital haemolytic jaundice and sickle cell anaemia, but not of Mediterranean anaemia, in which fluctuations in severity do not take this form. The crises are of various types but are all characterized by abruptness of onset, relatively short duration, and tendency to spontaneous recovery. They may be purely haemolytic in nature as is usual in congenital haemolytic jaundice, less commonly they may be erythroblastic, or, as is usual in infancy and early childhood, made up of a combination of these two processes. Sometimes the crisis may be in the form of abdominal pain without change in the blood picture. Such attacks have not been described in infancy. Occasionally a crisis may be prolonged or may be repeated at such short intervals that recovery from one has not taken place before the next one occurs. In my own

<sup>4</sup> It is impossible in this review to go into details or to describe all aspects of the constitutional types of haemolytic anaemia. I have attempted merely to emphasize certain features that have been brought to light in the recent literature, and that have a bearing on the clinical picture as it is encountered in infancy, as well as on the similarities and differences between various members of the haemolytic-erythroblastic group.

experience, severe, prolonged crises are more likely to appear in the winter and early spring—the season of infections

Haematologically the crisis is characterized by two phases (1) A period of increased blood destruction coming on abruptly and responsible for a fall in red cells and haemoglobin before the marrow can compensate for it, (2) Period of repair in which regeneration may be marked. If, as is usual, the blood destruction subsides rapidly, regeneration may be in its turn relatively unopposed and the return to the original level may be extraordinarily rapid

4 Apart from the crisis the red cells and haemoglobin tend to remain at a level which is characteristic of a given patient over a given period. That is, there seems to be a tendency to reach a certain degree of equilibrium which varies with the individual. This equilibrium is most stable and at a level at which fairly normal development is possible in congenital haemolytic jaundice, it is least stable in Mediterranean anaemia. In sickle cell anaemia it rarely reaches a point consistent with normal development, though continued life is possible

5 The cardiac manifestations form an important group of symptoms in the haemolytic erythroblastic group anaemias especially in sickle cell anaemia. In addition to systolic murmurs there may also develop a diastolic murmur and in some cases cardiac enlargement. Except for the systolic murmur these changes are rare in infancy but occasionally an infant has died as a result of acute cardiac failure, when previous examination had failed to reveal any apparent cardiac involvement

6 *Bones and skeletal changes* (225, 247, 445, 700) There has been a tendency to regard certain changes in appearance of the x-rays as diagnostic of so called "erythroblastic anaemia." To some extent this attitude is justified since it is rare except in Mediterranean anaemia to find bone involvement of sufficient degree to give the characteristic x-rays. But actually the same changes have been described both in sickle cell anaemia and in congenital haemolytic jaundice, as well as in other cases with erythroblastosis (225, 247). A certain amount of chronicity appears to be necessary for the development of changes in the skull, which are consequently rarely seen in infancy. The less characteristic alteration in the long bones is, however, not infrequent in early life

(a) *Congenital haemolytic jaundice* This is in general the mildest of the "constitutional" types. The blood picture is ordinarily the result of increased haemolysis and compensatory regeneration with little tendency to immaturity. Reticulocytes are usually between 10 and 20 per cent but may at times be much higher, especially in a crisis. Nucleated red cells are occasionally present and may increase in numbers during or just following a crisis.

In infancy the picture is somewhat different from that in older children or adults. Unfortunately not many cases studied in infancy are on record, although it is apparently not so very uncommon for the disease to manifest itself first before the end of the second year of life. The special characteristics of the disease in infancy may be summed up as follows: (1) Jaundice may be absent even in the presence of considerably increased blood destruction (286, 340, 749, personal observ), (2) The first appearance of the disease may be in the form of a crisis which is sometimes of great severity and may end fatally (572, 592), or may be less severe and clear up completely leaving nothing by which the condition may be recognized (277, Personal observ), (3) The blood picture may simulate the usual infantile picture of the haemolytic-erythroblastic group usually classed under the von Jaksch syndrome. Erythroblastosis has been present in every reported case. The white cells have occasionally been greatly increased in number, and predominance of lymphocytes is not uncommon, (Grob, white cells 85,000 with 83 per cent lymphocytes, De Rudder and Wesener, white blood cells 59,000, Herz, white blood cells 16,000 with 84 per cent lymphocytes, Hampson and Warner white blood cells 30,000 with 70 per cent lymphocytes) but there has been very little tendency to immaturity. In no case has there been leukopenia or any statement that platelets were reduced. (4) While the characteristic picture of anisocytosis with predominance of microcytes is usual also in infancy, occasionally macrocytes may be present in considerable numbers (572, 592). (5) The spleen is often not so greatly enlarged relatively as it is later on. Cardiac manifestations are not sufficient to attract attention. One child died of cardiac insufficiency in whom a short time previously the heart was not considered to be abnormal (249).

(b) *Sickle cell anaemia* The recognition of sickle cell anaemia should offer no difficulty, provided of course that its occurrence is kept in mind. The disease shows the characteristics of haemolytic anaemia of constitutional origin which have already been discussed. Jaundice may often, however, be so slight as to be missed, especially since patients are colored. In view of the frequent difficulty of recognizing anaemia in a colored child, and the fact that very often these patients are brought under observation because of symptoms that ordinarily do not lead to examination of the blood, sickle cell anaemia may be missed unless especially remembered and looked for.

Reticulocytes are regularly increased, ordinarily up to 10-15-20 per cent, during crises up to 40 to 50 per cent or even higher. Color index tends to be about 1 or above though a low color index may sometimes occur. White cells are moderately increased and there may be moderate shift toward myelocytes, but any marked degree of immaturity is rare. Not infrequently during crises lymphocytes are increased. Platelets are rarely reduced below 100,000. Erythroblastosis is more common than in congenital haemolytic jaundice, and at times may be extreme (over 100,000 per cubic millimeter), but the immaturity of the erythroblasts is rarely great and megaloblasts do not occur. "Hypoplasia" I have never seen nor has it been reported in any case in the literature.

From my own experience and from the scarcity of reports in the literature active sickle cell anaemia must be rather rare in the first year. During the second and third year of life, however, it becomes increasingly common, and it is not improbable that the great majority of cases are already established before the end of the second year. The characteristics of the disease at this time of life (15, 49, 405, 466, Personal observ.) are the following — (1) The onset of the active stage is often associated with a crisis or series of crises that are likely to be severe. Abdominal pain has not been present in my experience but pains in the extremities may occur. (2) *Cardiac manifestations* so common later on are less likely to be present in infancy. (3) The *spleen* varies in size in many cases, being greatly enlarged during crises, and barely palpable in quiescent periods. (4) The *blood* shows the same characteristics as later on except that the anaemia may be



more severe, the white cells somewhat higher and more labile, lymphocytosis more likely to occur, erythroblastosis more common and more severe, occurring not only during but also between crises

Before leaving the subject of sickle cell anaemia it is well to call attention to two facts (1) the disease may occur in the white race, (118, 119, 584), (2) it may be accompanied by considerable delay in somatic development (118)

Space forbids listing a complete bibliography of sickle-cell anaemia. Almost every article contains such a bibliography. The case reports leave much to be desired, however, and in preparing this brief account I have drawn on my own experience which comprises about two dozen cases as yet unreported.

(c) *Mediterranean anaemia* (Cooley) This type of anaemia belonging to the haemolytic-erythroblastic group has been clearly enough differentiated on clinical grounds to permit its acceptance as a clinical entity (42, 123), but it must be admitted that the clinical picture is only the end result of a process or group of processes which constitute the real disease and of which we have at present a very inadequate conception. The picture is characterized by anaemia, often of relatively low color index with erythroblastosis out of all proportion to the severity of the anaemia, occurring in a child of Greek or Italian parentage. The haematologic picture is that characteristic of the haemolytic-erythroblastic group —anisocytosis, poikilocytosis, increase in reticulocytes but not usually as great as in congenital haemolytic jaundice (121). The immaturity factor is not as great as one might expect from the degree of erythroblastosis, nucleated red cells may exceed 100,000 per cu mm but megaloblasts are relatively few, and immature white cells below the stage of myelocytes are rare (121). In numbers the white cells are usually increased and occasionally may reach figures above 50,000 (209, 725). Generally the predominant cell is the polymorphonuclear but sometimes, especially in infancy lymphocytes may predominate. *Platelets* are only occasionally reduced. *Resistance* is normal or there may be moderate increase in the span.

While increased haemolysis is probably always present, it is usually of minor importance (42, 121, 725), and outspoken jaundice is rare. The spleen is generally enlarged, sometimes greatly so, while enlarge-

ment of the liver is usually only moderate. Cardiac involvement is common, and cardiac failure is sometimes a cause of death. Abdominal pain occurs, but rarely if ever in crises which dominate the picture as in congenital haemolytic jaundice or sickle cell anaemia. The onset of the disease is gradual and frequently occurs in infancy. The characteristic osseous changes have already been considered.

Up to the present the majority of cases have been published in America. In Italy of late years a form of familial haemolytic-erythroblastic anaemia has received increasing attention. These cases are closely similar to the American ones, in many ways, but the Italian authors have failed to record changes in the bones or in the contour of the skull or face. For this reason the Italian cases have not been considered examples of what Cooley described.<sup>5</sup> As was stated above we know nothing of the mechanism by which the clinical picture is produced, and nothing of the fundamental nature of the disease. The clinical and haematological picture is merely the surface and from it we must attempt to guess at what is going on. To reject the Italian cases because one detail is missing appears to me a mistake when in all essential ways the Italian cases fit the picture which has been described in the American cases. The Italian cases are in general more severe than the American and have usually been fatal before the end of the second year. The lower age of the Italian cases may partially explain the lack of skeletal changes, and "mongoloid" facies. In one group of cases (Cerza) the color index tended to be higher than in the others. The slightly greater incidence of lymphocytosis probably is due to the lower age group. Myeloblasts or lymphoblasts have been encountered a little more frequently possibly than in the American cases. It is interesting in view of Cooley's remarks on the subject that the great majority of these reports come from southern Italy and Sicily (Marcialis (Sardinia), Rossi, (Apulia), Cerza, Auricchio, Lattes (Naples), Prebil (Messina), Mondini, Vasile (Palermo)).

(d) In addition to the three well defined syndromes among the cases of haemolytic-erythroblastic anaemia of constitutional origin there are other cases that appear to depend on a strong constitutional factor but which for some reason do not appear to fit into the well

<sup>5</sup> In the past year or two cases satisfying the criteria of this form of anaemia have appeared in the Italian literature mostly as brief society reports.

defined groups just described. The attempt is continually being made on the basis of some symptoms or sign common to a number of cases to separate out a group which can be treated in common and be given a special pigeon hole. In most of these no common factor of importance has yet been demonstrated, but rather some superficial characteristic that serves in the nature of a clip or elastic band. Nocturnal haemoglobinuria is such a characteristic serving to tie together a very interesting group of cases, of apparently constitutional origin. Hemosiderinuria is another, to which Marchiafava's name has been attached. Cold-haemolysis producing the so-called paroxysmal haemoglobinuria is a third example. The fact that in this case a common etiology has been found for the great majority in congenital syphilis serves at the same time to give this group a real standing among the haemolytic diseases, as well as to take it out of the primarily constitutional group. It must be remembered, however, that in not every case of haemoglobinuria with cold-haemolysis has syphilis been demonstrated.

## *2 Haemolytic-erythroblastic anaemia of extrinsic origin (chronic cases)*

This designation covers a large group of cases occurring primarily in infancy to which the terms "von Jaksch" syndrome or "anaemia gravis" have been applied. While extrinsic factors play a large part in the etiology of most cases, it cannot be denied that constitutional factors are also present. The mere fact that a particular age is especially susceptible points to an intrinsic factor, but in addition, cases are reported in several members of a family consecutively. Thus, the border line between these cases and those primarily constitutional such as have been reported so frequently in Italy is not a sharp one. Likewise there are transitional cases to the non-erythroblastic hypochromic anaemia due largely to iron deficiency, and to that group of cases to be discussed under acute haemolytic anaemia.

In the clinical picture there is little that is distinctive, but a mixture of symptoms and signs, some due to the anaemia, some to the fundamental condition of which the anaemia itself is a symptom. The onset is usually insidious and it is often only some acute episode that brings the infant under observation. The skin often has a yellowish

palor termed subicteric sometimes described as muddy, outspoken jaundice is not common. Petechial haemorrhages are present in many cases, and occasionally larger purpuric patches. Edema may be present over the lower extremities. Cardiac manifestations, including diastolic murmur and enlargement, may be present, and occasionally death may be due to cardiac failure. The spleen is usually enlarged, sometimes to a great extent, but there seems to be no relation between splenomegaly and the severity of the anaemia. Enlargement of the liver is rarely more than moderate. Enlargement of the lymph glands while frequently present has little special significance at this age.

In the blood the outstanding features are the great reduction in red cells, and the tendency to erythroblastosis. Reticulocytes are usually moderately increased and there is present polychromasia, but reticulocyte counts above 15 per cent are infrequent. Color index is above 0.8 in most cases and may be very high. Anisocytosis is present with many macrocytes and the average cell size is usually above the normal. The nucleated red cells are of all grades of immaturity and "megaloblasts" are frequently found as well as mitotic figures. The *white cells* are usually moderately increased but extreme leukocytosis with counts above 100,000 have been reported (549). The tendency to great increase in white cells is seen especially in the newborn period. Marked immaturity among the white cells occurs, but is not common (see table 12). Relative reduction in neutrophils and a relative and absolute increase in lymphocytes is frequently observed. Immature lymphocytes may occur but lymphoblasts are rare. *Platelets* are reduced in the great majority of cases in which they have been mentioned and in many cases the reduction is extreme.

There are two variations of this picture that deserve mention, one might be designated "pseudo leukaemic" (table 12) the other "neutropenic" (table 13), though these are not the best terms that could be devised. The first of these variations has been separated out on the basis of the presence of a high percentage of immature white cells. In this group there is also a tendency to a marked erythroblastosis, and leukocytosis. The cases are for the most part associated with syphilis or severe infection and the mortality is especially high. The variation designated "neutropenic" is separated on the presence of a neutrophil reduction to below 2,500. In this group erythroblastosis

TABLE 11  
*Anaemia of infancy—haemolytic-erythroblastic type*

	AGE	JAUNDICE	HAEMORRHAGE	LIVER	SPLEEN	BLOOD					TREATMENT	OUTCOME	
						Red blood cells $\times 10^6$	Haemoglobin (C1)	White blood cells $\times 10^3$	Neutrophils	Erythroblasts			
Marquard	2y	—	0	0	+	2 1	30 (0 75)	6 3	37	++			
Stoeltzner	2y 22m	—	0	0	++	4 1	44 (0 54)	7 0	35	++			
		±		+	++	1 6	20 (0 6)	9 3		++			
Baar u Stransky	15m	±	0	—	++	2 7	35 (0 65)	15	54	7/100			
Rohmer	14m	—	—	—	—	2 2	38 (0 85)	10	30	12/100			
Petterson	12m	—	+	+	++	1 8	35 (1 0)	16		+			
		—	nose	±	0	1 7	42 (1 3)	15	35	++			Pyelitis
Opitz	12m	—	—	±	—	2 5	34 (0 7)	20	69	12/100	Liver Transf		W
Cooley and Lee	11m	—	—	+	—	3 4	40 (0 6)	11	37	44/100	Transf		W
Clodius	12m	0	0	+	++	1 8	3 7 (1 0)	7 6	42	+			W
Hampson and Warner	11m	+	0	0	++	2 0	36 (0 9)	8 1	50	5/100			W
Vasile	10m	—	—	+	++	1 6	26 (0 8)	28	34	13/100	Liver Transf		W
Moncreff	8m	—	±	+	++	2 1	15 (0 35)	23	23	22/100	Transf		W
Cooley and Lee	7m	±	Purpura	+	++	2 0	30 (0 75)	24	23	5/100			
		±	—	+	++	1 2	21 (0 9)	14		24/100			
Baar u Stransky	6m	±	Petech	+	++	1 5	30 (1 0)	19	30	15/100			
de Lange	5m	—	—	+	+	1 4	21 (0 75)	18 7	22	11/100			
Baar u Stransky	4m	±	Petech	+	++	0 8	20 (1 25)	15	27	8/100			
Parsons, Hawksley and Gittins	4m	±	±	+	++	2 0	45 (1 2)	15			Transf		D
Parsons, Hawksley and Gittins	3m	0	±	+	+								D
Faber	3m	±	Purpura	+	+						Liver		Im-proved

TABLE 12  
Haemolytic-erythroblastic anaemia of infancy—"pseudoleukaemic type"

	AGE	JAUNDICE	HAEMORRHAGE	LIVER	SPLEEN	BLOOD					TREATMENT	OUTCOME	
						Rcd blood cells	Haemoglobin	White blood cells	Neutrophils	Lymphoblasts			
Guy Griffiths	2y	+	-	+	0	1 0	18 (0 90)	10	64	+	Myelocytes 13%, megalo- blasts +	W	
Knauer	13m	±	0	++	++	0 92	18 (1 0)	11	+	+	Immature white cells, platelets normal	?	
Parsons and Hawasley	11m	-	+	±	++	2 1	16 (1 1)	15 4	37	+	Platelets reduced, imma- ture white cells		
Clodius	12m	±	0	+	++	1 4	34 (1 2)	15 7	36	+	Myelocytes +, megalo- blasts ++	D	Infection
Dessyllia	8m	-	0	+	±	2 3	31 (0 65)	4 5 67	38	++	Myelocytes 30%, mvelo- blasts 5%, platelets reduced	D	
Wengraf		+	+	+	++	3 1	50 (0 80)	14	25	++	Myelocytes, myeloblasts, megakaryoblasts, platelets 100 000	D	Syphilis, sepsis
Brannan	7m	±	-	++	++	1 3	30 (1 15)	5 5	30	++	Myelocytes 5%, melo- blasts 15%, platelets reduced	D	Infection
Seckel	7m	±	-	±	++	2 4	35 (0 73)	10 ±		++	Myelocytes +, megalo- blasts ++	D	
Smallwood	5m	+	+	+	++	1 8	46 (1 3)	13	27	+	Immature lymphocytes, megakaryoblasts, platelets 1800	?	
Watson Hoff	2m 2m	- -	- -	- -	- -	2 8 2 7	44 (0 8) 47 (0 85)	72 23	33	++ ++	Immature white cells Myelocytes 12%, myelo- blasts	D D	Syphilis, Syphilis, sus Syphilis
Baar u Stransky	4w	-	-	++	++	1 4	32 (1 15)	10	21	++	Myelocytes 10%, myelo- blasts 18%, megakaryoblasts ++	D	

TABLE 13

*Haemolytic-erythroblastic anaemia of infancy—cases with neutropenia*

	AGE	JAUNDICE	HAEMORRHAGE	LIVER	SPLEEN	BLOOD						TREATMENT	OUTCOME	Goat's milk? Syphilis? Goat's milk
						Red blood cells	Haemoglobin (color index)	White blood cells	Neutrophils	Erythroblasts				
Nussbaum	3y	±	—	++	++	1 5	35 (1 2)	3±	Low	+	Platelets 63,000		?	Goat's milk?
Frank	2y	±	—	0	0	1 3	— (1 7)	4 3	33	1/100	Platelets 90,000		W	
Mensi	2y	±	—	±	0	1 4	20 (0 75)	10	18	9/100			D	
Hawksley	23m	—	—	++	++	1 8	35 (1 0)	6 3	39	22/100		Splenectomy	Imp	
Roth				0	0	0 98	22 (1 1)	2 8	34	0			W	Goat's milk
Mensi	15m	±	—	±	0	0 8	15 (0 95)	6 2	31	±	Platelets reduced		?	
Opitz	14m	—	+	+	0	1 8	51 (1 45)	4 5	37	0	Platelets 70,000		W	
Cooley and Lee	10m	—	—	—	+	1 6	36 (1 12)	4 1	34	4/100	Platelets 40,000, meg-aloblasts	Transf	W	
Cooley and Lee	10m	—	—	+	+	1 2	36 (1 5)	12 4	20	4/100	Platelets reduced, meg-aloblasts	Transf	W	
Faber	9m	0	0	±	±	0 65	16 (1 2)	8 1	33	16/100	Megaloblasts	Liver	W.	
Parsons and Hawksley	9m	—	±	++	++	1 6	30 (0 95)	6 0	35	6/100	Platelets 14,000	Transf	W	
Ducas and Jacquet	8m	—	0	0	0	2 3	35 (0 8)	4 7	37	0			?	
Mensi	7m	—	—	++	++	1 5	35 (1 2)	4 2	51	++	Megaloblasts		D	
Parsons and Hawksley	6m	+	—	—	—	1 8	35 (1 0)	5	"Few"	±			D	
Cooley and Lee	5m	0	±	—	—	0 89	30 (1 7)	3 7	37	6/100	Platelets reduced	Transf	W	
Cooley and Lee	5m	—	—	+	+	1 2	28 (1 2)	12 6	9	15/100	Platelets reduced, meg-aloblasts	Transf	D	
Cooley and Lee	4m	—	—	—	—	1 5	30	4 8	36	3/100		Transf	W	

is relatively much less marked than in the "pseudoleukaemic" group, and the color index tends to be high. Severe infection plays a much smaller part in the etiology and the prognosis is relatively better.

Etiologically the most important factors may be grouped under infection and nutrition, to which may be added constitution. In early infancy syphilis and sepsis or the two combined account for a large proportion of the cases. Later in infancy the etiological factors producing hyperchromic-erythroblastic type of anaemia are not yet clearly understood. In Germany most writers have blamed "constitution" while in France they have tended more to implicate syphilis even in the absence of positive evidence. The most hopeful progress has come from the study of a possible deficiency factor in goat's milk anaemia.

The importance of goat's milk anaemia lies in the fact that the von Jaksch picture appears to be more common in infants fed on goat's milk than in those fed on cow's milk, (29, 35, 79, 80, 203, 227, 241, 402, 509, 517, 591) especially that described as "pernicious" by which is meant high color index, macrocytosis, presence of megaloblasts, thrombopenia and often leucopenia. Gyorgy has succeeded in curing his cases with liver and with yeast extract (259, 260). As regards the former, there is nothing unusual in the cure of cases belonging to the erythroblastic-haemolytic group with liver and a rise in red cells and even in reticulocytes does not necessarily mean a deficiency of some factor present in liver, any more than a rise in reticulocytes after iron in the first few weeks of life means a deficiency of iron. It is suggestive, however, and points the way to a possibly fruitful field for investigation.

Another interesting fact that may have some bearing on the etiology is the geographical distribution and the diminution in the number of cases reported from Germany. When Kleinschmidt (339, 341) and Schwenke (619) originally reported their large series a very high proportion of the cases belonged to this group. Similar cases were reported up to about 1925 but since then the number has fallen off. Allowing for the fact that a number of Schwenke's cases were of goat's milk anaemia and that this picture is too well recognized now to make the reporting of large series profitable, there still is reason to suspect that there has been a change in the type of anaemia in Ger-



many Kleinschmidt's (343) change of attitude toward the value of iron might also be explained on the basis of a change in the type of anaemia. The fact that the greatest number of cases were reported during the war and the post-war inflation years, when there was an increase in other deficiency diseases in Germany and Austria indicates that there may be some deficiency factor responsible for this type of anaemia, a fact long ago stressed by Aron (22) who pointed out that the diet used by Kleinschmidt was not only low in milk but also high in "accessory factors." At no time have these cases been common in America or England; but in Italy at the present time there are many reports.

In addition to infection and nutritional factors, there are a few other conditions reported to cause the "von Jaksch" picture. In conditions associated with bone marrow replacement erythroblastosis may occur as well as leukopenia and thrombopenia. *Osteosclerosis*; *Neuroblastoma* with bone marrow involvement (rare before the third year), *Xanthomatosis* (rare before the third year), *Hodgkin's disease* may cause a haemolytic type of anaemia with erythroblastosis, *Lead poisoning* is frequently accompanied by the appearance of erythroblasts although such cases in infancy are rare.

### 3 *Acute haemolytic anaemia*

There is nothing new in the occurrence of acute or subacute haemolytic anaemia (740). The service that Lederer (392, 393) performed was not to describe something that was previously unknown, but to demonstrate that transfusion had a specific curative effect. He was also responsible for the introduction of a new name which had the merit of being short and to the point. When we come to the matter of definition, however, we begin to enter the interminable arguments over boundary lines. It is the old story of the attempt to divide off the area of the haemolytic anaemias into little fields each neatly named and bounded, as if each were a little piece of private property.

Acute haemolytic anaemia is a state of affairs brought about by a number of etiological factors, of which infection, allergy, and intoxication are the chief. The course of events is about the same whatever the etiology, and is very similar to that of a crisis of congenital haemolytic jaundice with which it may easily be confused (57, 145, 488).

The following types are described

1 Associated with infection (a) The ordinary increased hemolysis of infection which may in rare cases be severe enough to cause a dangerous fall in haemoglobin, but is usually a rather minor occurrence

(b) A form in which the severity of the haemolytic process and the consequent fall in haemoglobin and red cells is out of all proportion to the severity of the infection (This is the type to which Lederer called attention)

(c) Miscellaneous cases of haemoglobinuria associated with various infections A separate classification should not be made for this group I have done it at this point merely because in the literature there appears to be no realization that (b) and (c) belong together

2 Paroxysmal haemoglobinuria (cold haemolysis)

3 Favism which appears to be a form of allergy to the fava bean of Sardinia and Sicily

4 Black water fever associated with malaria

5 Mismatched transfusion

The most important cases from the point of view of this work fall in (b) and (c), and these will form the basis of the description There are, of course, other causes of acute haemolytic anaemia, such as poisons of various types and other allergic materials In this article I am, however, not concerned with a complete review of the subject but only with the condition as it has been described in infancy

In the group to be described the patient who may be of any age becomes suddenly ill, usually with headache or abdominal pain, having previously been well Pallor and weakness develop rapidly, icterus usually appears and sometimes the haemolysis is sufficiently violent to cause haemoglobinuria In a period that may be anywhere from two days to two weeks the patient may be reduced to a dangerously anaemic state with air hunger, though not in every case is the crisis as severe as this Usually in such a state transfusion is necessary to save life and may have to be several times repeated Again after a period that may vary from a week or ten days to a month recovery takes place being completed in about a month's time and in most cases permanent In some cases transfusion has a most remarkable effect in cutting short the attack and initiating immediate recovery, in others one gains the impression that the transfusion has done no

more than prolong life to the point where spontaneous recovery begins. In many cases recovery has taken place without treatment

The red cells are greatly reduced, often to under a million (in one case as low as 600,000 with recovery), with usually high color index. Anisocytosis is present but not usually marked, and poikilocytes are rare. Reticulocytes are not increased at first, but appear after a week or more, a rise in reticulocytes being definitely associated with the onset of the recovery phase (106, 683, 717, 718, 530). Nucleated red cells are usually earlier in their appearance than the reticulocytes but often there is an increase not only in numbers but also in immaturity at the point of beginning recovery (106, 300, 683, Personal observ). They disappear rapidly as recovery takes place. The white cells may be increased sometimes to an extreme degree (Lazarus 108,000, 76,000 on the tenth and fourth day respectively, Lederer 52,000, third day, Kaiser and Bradford 61,000 fourth day). Myelocytes are usually present and are often increased at about the time of beginning recovery. In some cases the neutrophils are relatively reduced, in others the lymphocytes are greatly increased, but generally the differential count shows no changes of moment. The platelets are generally not affected, but occasionally there may be reduction. Because of the blood picture the older cases may be found under a variety of names of which the usual ones are "acute pernicious anaemia" and "leukanaemia." "Pernicious" pictures are, however, rare in childhood.

Haemoglobinuria (91, 164, 322, 502, 717) has been described a number of times but I have been unable to find any case with haemoglobinuria in babies under two years of age except possibly Ferri's case at twenty-five days and a group of cases occurring among the newborn going under the name of Winckel's disease and considered to be due to sepsis. "Cold haemolysis" as demonstrated in the Donath-Ladsteiner test has occurred in a few cases associated with infection and in which syphilis was not demonstrated (91, 322), but the Donath-Ladsteiner test has not been found positive under two years of age. Likewise paroxysmal haemoglobinuria has not been reported to my knowledge in any case below two years of age.

In a number of cases considered by the authors to be examples of acute haemolytic anaemia the resistance to hypotonic salt solution has

been diminished (300, 502, 683, 717) This raises a difficult point of diagnosis Are we possibly dealing in these cases with congenital haemolytic jaundice in which between crises the disease is entirely latent? On the other hand, in a number of these cases there has been a certain familial tendency or tendency to repeated attacks of acute haemolysis which suggests a constitutional factor (29, 271, 676) The normal fragility test has been considered by some to rule out congenital haemolytic jaundice while by others it is considered that congenital haemolytic jaundice may occur without increased fragility On the one hand, we have the question of specificity of the fragility test and on the other the diagnostic significance of the apparent complete normality of the blood between attacks The difficulty arises from the necessity of having to decide about the nature of the disease from the surface phenomena

The similarity of the crisis of acute haemolysis and that of congenital haemolytic jaundice is very great, the chief difference lying in the fact that in the acute cases the crisis occurs with a bone marrow at rest while in congenital haemolytic jaundice the bone marrow is already in a state of stimulation and therefore is ready to respond more quickly This is a possible explanation for the greater severity and the usually longer duration of the acute attack There may, of course, be other factors concerned with the haemolysis itself but as yet we know too little about the process of hemolysis and its control to do more than indicate a possible line of attack The specificity of transfusion in some of the cases is an important phenomenon that should receive attention from this point of view

The other forms of acute haemolytic anaemia need little comment Favism (53, 437, 444) is almost unknown outside of Italy The cases occur in May and come not only from eating the raw Fava bean but also occasionally from passing near a field in which the beans are growing It is apparently an allergic phenomenon and the attacks have been described mostly in young children, and occasionally in infancy The attack may commence a few minutes after eating the bean It is extraordinarily severe while it lasts, often causing haemoglobinuria, but the attack is self-limited and the mortality is low The sequence of events is essentially the same as that described above, except that the haemopoietic tissue usually shows signs of activity

somewhat earlier and recovery may set in more quickly. The chief interest lies in the fact that the attack is allergic in nature, and that therefore other attacks of acute haemolytic anaemia may be on an allergic basis, a possibility that up to the present has received no attention.

Acute haemolytic anaemia has been described after vaccination (708, 733) following gas poisoning (676), and after eating "Rausch-beeren" (206). It is quite possible that some form of allergy was a factor in these cases.

#### B HYPOPLASTIC-APLASTIC TYPE OF ANAEMIA

The cases belonging to this group are characterized haematologically by (1) Anaemia with color index usually in the neighborhood of 1.0, (2) Absence or reduction of the signs of regeneration, (3) Little if any tendency to immaturity, (4) Usually reduction in the white cells and platelets. Clinically, they are often the most distressing cases with which we have to deal as they progress to the almost inevitable fatal ending. Pathogenically they are the most obscure of all the forms of anaemia, and not even a beginning has been made in successful investigation.

In recent years there has been an increasing tendency to group together with the cases of anaemia those of neutropenia and thrombocytopenia in which there is evidence that the reduction of these elements is due to failure on the part of the marrow tissue to manufacture them (83, 243, 395, 390, 691). This must be regarded for the present as a mere classing together of all cases in which there is any evidence of haemopoietic inadequacy, and does not imply that the process causing this inadequacy is the same in all cases. The manner in which the hypoplasia develops is entirely unknown, but it is not unlikely that there are two separate processes: (1) An involvement of the bone marrow itself, and (2) a disturbance in the regulation of blood formation. Until we know more of the manner in which haemopoietic activity is regulated it is useless to discuss these possibilities, or to attempt to classify the conditions under which hypoplasia occurs according to them. The most that can be done at this time is to name the most important of these conditions.

1 *Infection*. As has been indicated in the section on infections,

an aregenerative picture is often encountered in their course. The severity is usually not great and may consist in no more than a failure of a reticulocyte response to administration of iron. Occasionally, on the other hand, the hypoplasia may be severe and may include not only the erythropoietic elements but also the white cells and platelets. In such cases the prognosis is bad. Death may result from fatal haemorrhage but usually is due to the severity of the infection, or to the gradual wearing down of resistance. It is almost never due to the severity of the anaemia, and treatment is directed toward combating the infection itself rather than the hypoplasia which is merely one pathological process among many.

2 *Anaemia of the haemolytic-erythroblastic group* The hypoplasia occurring in this group has already been pointed out. In its mildest form it consists in platelet reduction which is common in the cases due to extrinsic factors or infection, but does not occur in the constitutional types. In a smaller number of cases neutropenia may occur. Rarely there may be a progressive development of a hypoplastic picture with diminution in the signs of erythropoietic activity and finally a fatal outcome. These changes have been in the past attributed to "exhaustion" of the bone-marrow. Terminal aplasia does not occur in the constitutional types, so that it is more likely that such are generative pictures are due to increasingly severe haemopoietic involvement, i.e., a failure of maturation affects a progressively earlier stage of differentiation until finally there is no development whatever beyond the most primitive undifferentiated cell. This is an attractive hypothesis and Witts (740) brings evidence in its favor, but more proof is needed. If it is so, then it is probable that the reason we see no more of it is that the patients in whom it might develop die as a result of intercurrent disease before the final aplastic stage is reached.

3 *Acute leukaemia* The aplastic anaemia occurring in acute leukaemia has been attributed to replacement of the normal bone marrow with the leukaemic tissue, as in the case of tumor metastases. Jaffe presents evidence against this idea. It is possible that the tissue from which the cells of the blood develop becomes progressively involved in the leukaemic process, and is thereby prevented from differentiating in the usual direction. The return of the blood toward a more normal state during a remission supports such an hypothesis.

4 *Extrinsic factors* capable of causing hypoplastic pictures are especially poisons, x-rays and radium. I have not found any reports of cases due to these agents in infancy. While the absence of reports is no reason for excluding the possibility, lack of opportunity for exposure would render anaemia from these causes extremely unlikely. Arsphenamine poisoning of course should be kept in mind.

5 *Conditions involving the spleen and reticulo-endothelial cells*. This is the group to which the term "splenic anaemia" is usually applied. There is no harm in the term, and it can actually be quite useful in holding together this very group. If it is to be used for this purpose, however, it must not be used indiscriminately as a scrap-heap for every obscure or inadequately studied case in which anaemia occurs with splenomegaly.

In this group we have a number of conditions, including cirrhosis of the liver, Gaucher's disease, splenic vein thrombosis (Banti's disease), "reticulo-endotheliosis," Hodgkin's disease, in which a hypoplastic picture may occur associated with splenomegaly. In some of the cases it has been found that splenectomy may be followed by a return of the blood picture to normal. This has led some observers to the hypothesis that the spleen in those conditions exerts an inhibiting influence on the activity of the bone marrow leading to hypoplasia. In many of these cases, however, the bone marrow is involved in the disease process, so that it is doubtful whether we deal with direct bone marrow injury or a disturbance in the control of haemopoiesis. A case such as that reported by Ullrich in which in Gaucher's disease after splenectomy the blood picture improved while at the same time the marrow involvement became greater inclines one to the latter hypothesis.

As has been pointed out in the sections dealing with these conditions, hypoplasia is rare in infancy except in reticulo-endotheliosis, the course of which is more acute than that of the others. Hypoplasia occurs much less frequently in xanthomatosis and Niemann-Pick disease.

6 *Cases in which the cause is obscure or in which constitutional factors are predominant* (243, 395, 691). Because of our almost complete ignorance concerning the mechanism by which these cases develop, we can do no more than group them into a number of clinical types based on the course and the blood picture.

(a) Acute aplastic anaemia (aleukia haemorrhagia, Panmyelophthisis) In this there is a rapid "melting away" of all the bone marrow elements, associated with necrotic angina and a tendency to haemorrhage from the mucous membranes. Death occurs in about ten days or two weeks, and transfusion has little effect except to prolong life by a few days. Septicaemia may be present. It is usually not possible to determine the sequence of events, whether the infection or the aplasia was first but most observers incline to the latter view. Aplasia by itself cannot account for the rapidity with which the anaemia often develops, so that we must infer some other process. Haemorrhage could account for the anaemia, but in one case that I was personally able to study, a transfusion was almost immediately haemolyzed so that the possibility of increased destruction of blood must be taken into consideration. The condition is very similar clinically to acute leukaemia, from which it may often be differentiated only with the greatest difficulty. The diagnosis is important, however, for occasionally repeated transfusions are followed by recovery.

Acute aplastic anaemia rarely if ever occurs in infancy, except clearly as a result of sepsis (59, 148, 334, 556, 594).

(b) Agranulocytosis This has been reported a few times in infancy unaccompanied by anaemia and thrombocytopenia (110, 243, 594, 608, 732, 742), but in the great majority it is part of a general hypoplastic picture associated with infection.

(c) There are a number of cases of chronic "hypoplastic" anaemia of obscure origin occurring usually in older children, which begin gradually and progress slowly, with exacerbations and remissions, usually to a fatal termination in the course of months or years. Some of them develop in relation to an infection, successful elimination of which may bring about a remission, but usually the downward progress is renewed and cannot be halted (30, 384, 395, 450).<sup>\*</sup> Transfusion may bring about a remission and occasionally repeated transfusions have caused an apparent cure, but the chronicity of the condition is such that recovery should be viewed with skepticism unless it has lasted for a matter of several years. Instances of this type have been reported in children less than two years of age (60, 243, 514, 687, 691).

<sup>\*</sup> These examples by no means cover the literature on this type of case.



(d) A few cases depending clearly on constitutional factors have been described. Fanconi's "Perniciosa-ähnliche Anämie" with atrophy of the testicles and familial occurrence belongs here. Leeuwen has reported a similar case. Another type definitely constitutional is represented by two cases seen at the Harriet Lane Home. In these there was an aplastic anaemia confined to a failure of erythropoiesis so marked that the children could be kept alive only by means of transfusions administered every month or six weeks. One child had been so kept alive for eighteen months, the other for four and a half years, and during several periods of observation there was never a sign of regeneration. I have seen the clinical records of another similar case also kept alive by transfusions but in whom the haemoglobin could be maintained at a higher level and with evidence of reticulocyte response. A case reported by Langer probably also belongs to this group.

#### C HYPOCHROMIC ANAEMIA

This is the common anaemia of infancy, in this country at least comprising nearly all the cases classed as nutritional or nutritional-infectious. Reduction in haemoglobin is the outstanding and often the only characteristic. The *red cells* are smaller than normal, *anisocytosis* is moderate, *poikilocytes* are rarely encountered. *Reticulocytes* depend roughly on the severity of the anaemia, being only rarely increased as long as the haemoglobin remains above 7 grams per 100 cc and rising to between 3 and 5 per cent as the haemoglobin falls below 4 grams per 100 cc. They vary from day to day and any infection may cause their temporary disappearance. A reticulocyte count of over 5 per cent in the absence of specific marrow stimulation is evidence that blood destruction is increased above the usual amount encountered in these cases. *Nucleated red cells* are at most only occasionally seen in the typical case, but there is no sharp line to be drawn between the normal and the abnormal. Of course, by definition any increase above the usual places the case in the haemolytic-erythroblastic group regardless of color index but in the majority the color index tends to be above 0.8 in the presence of erythroblastosis. (An exception is found in "Mediterranean anaemia" in which the color index tends to be low)

There is nothing characteristic about the *white cell picture*, which is determined by the condition giving rise to the anaemia. The *platelets* are not affected.

Clinically there is little to characterize these patients except their *pallor*. Pallor, however, is deceptive and one can not estimate the severity of the anaemia or in some cases even the presence of anaemia by the degree of pallor. Parsons has used the statement of the parents that the child was pale from the time of birth to draw important conclusions. This is equivalent to accepting hear-say evidence; it may be true, but it is not proof. *Haemorrhages* and *edema* do not occur except as part of the picture of the underlying condition, such as infection or nutritional deficiency. *Cardiac manifestations* are rare except for a systolic murmur which clears up with recovery from the anaemia. The *spleen* is sometimes slightly, rarely greatly, enlarged.

These patients show surprisingly little disturbance from their anaemia even when the haemoglobin is below 20 per cent (3 grams per 100 cc. more or less). *Loss of appetite* is perhaps their most outstanding symptom, and one which contributes materially to the condition of the child as already described. Another thing that has received too little attention, although recognized by Kleinschmidt in 1916 is the *psychological make-up* of many of these children—they resist any change from the habitual or any new departure. Weaning, the first use of solid food, even a change of room or of regime in a hospital may be met by a stubborn refusal to eat. It is difficult to say how far this is a result of the anaemia, but there can be no doubt of its effect in delaying recovery. The *nutrition* of infants with hypochromic anaemia is generally good, in contrast to the poor condition of those with hemolytic-erythroblastic type, and it is not improbable that a good gain in weight contributes toward intensifying the fundamental deficiency. Increased *susceptibility to infection* has already been emphasized. *Death*, rarely, if ever, occurs as a result of the anaemia, but is usually due to intercurrent infection, especially pneumonia.

#### *Nutritional-infectious group of anemias*

In the first section of this review I have presented the common background from which anaemia develops, in the second section, the etiological factors which influence the haemoglobin level and contrib-

ute to the development of anaemia were discussed in detail, in the third section the various clinical and haematological pictures have been given, classified on the basis of the pathological process. In this summary I shall attempt to discuss the relation of the etiological factors to the development of the varied forms which are assumed by anaemia belonging to the nutritional-infectious group, which accounts for probably nine-tenths of all the anaemia encountered in infancy.

As has been indicated the anaemias belonging to the nutritional-infectious group fall into two general types, the hypochromic and the hemolytic-erythroblastic, but there are all manner of gradations between the two, so that we must look on them not as definite diseases each with its separate etiology, but as the end result of the interaction of many factors each exerting its influence on the processes of blood formation or destruction. The predominance of factors having one type of influence will naturally result in a picture quite different from that brought about by factors having a different influence.

In dealing with the mechanism by which a particular form develops, we must consider the following processes: (1) Deficient haemoglobin formation, (2) Deficient erythropoiesis in the sense of hypoplasia, (3) Deficiency of some factor responsible for the stimulation of haemopoiesis, (4) Deficient maturation of red cells, (5) Increased blood destruction.

(1) *Deficient haemoglobin formation* This is probably the chief factor in the development of hypochromia, and has been attributed by most to deficiency in the supply of iron. While iron deficiency is undoubtedly the most important single factor in the cause of hypochromic anaemia, there are other things to be considered. Deficiency in other materials used in the synthesis of haemoglobin has been postulated by many but never proved except possibly in the case of animals. Failure to synthesize haemoglobin is another factor which is only beginning to be studied following the demonstration of the necessity of copper for the synthesis, in animals at least. The therapeutic effect of copper in infancy indicates that the factor of faulty haemoglobin-synthesis may play a part in infants as well as rats. As has been already stated it is impossible to separate the problem of haemoglobin synthesis from that of the availability of iron within the body, i.e., iron may be unused because it is unavailable, or it may be

unused because haemoglobin is not being made (See part II—iron metabolism) The effect of inorganic iron may be to supply iron in a more immediately available form, or to stimulate synthesis of haemoglobin as well as erythropoietic activity

While hypochromia is almost by definition associated with deficient haemoglobin formation, it must be remembered that the latter may be masked by a marked fall in red cells, and cases are occasionally encountered in which a cure of the haemolytic-erythroblastic phase may leave the haemoglobin deficiency phase untouched so that the color index falls and iron becomes necessary to complete the cure

(2) and (3) *Deficient erythropoiesis and deficient stimulation of erythropoiesis must be considered together* In the so-called "hypoplastic" anaemia we are dealing with a function that cannot be stimulated We see some such effect in any infection, at least we draw such a conclusion from the failure of the reticulocyte rise following the use of liver or inorganic iron Except during the presence of an infection, however, "hypoplasia" is encountered only rarely in the nutritional-infectious group of anaemias Deficiency of some factor leading to adequate stimulation of erythropoietic activity is more common and frequently after an infection we may see little tendency to an increase in red cells or haemoglobin until iron is given and a reticulocyte rise occurs

(4) *Deficient maturation has already been discussed in relation to the haemolytic-erythroblastic group of anaemias* Factors leading to the development of erythroblastosis are imperfectly known Undoubtedly "constitutional" tendencies play an important part Young infants tend to react this way We have already seen that in congenital haemolytic jaundice erythroblastic blood pictures are the rule in infancy while later on they are exceptional There are, however, as we have seen, other etiological factors that may cause injury to haematopoiesis resulting in deficient maturation of erythrocytes and consequent erythroblastosis Severe infection is such a one More important to the present discussion is the probability that in many instances erythroblastosis may be determined by some specific deficiency, such as is presumably present in the case of the "pernicious" pictures in sprue or coeliac disease

(5) *Blood destruction* This is quite generally increased in the

cases belonging to the nutritional-infectious group. In the hypochromic cases it is a relatively minor factor, in the erythroblastic cases it is of greater importance and may in some be the principal cause of the anaemia, though this still awaits proof. Simultaneous determinations of urobilin excretion in the stools and reticulocyte counts over prolonged periods have shown a tendency to the presence of an equilibrium which is interpreted as an equilibrium between blood formation and blood destruction, such that when reticulocytes are in excess, the red cells tend to rise and when urobilin excretion predominates they tend to fall (314). The increased blood destruction has been used to support the idea of a toxic effect from the fat of milk. Recent studies (unpublished) have shown that increasing the proportion of fat in the diet to the point of ketosis does increase the output of urobilin but this increase is relatively minor in extent, and moreover in the cases of nutritional anaemia with increased urobilin excretion a cure of the anaemia with iron, while the child is maintained on an otherwise exclusive milk diet, is accompanied by a return of the urobilin excretion to normal values (314). Except for infection which usually causes a rise in the rate of urobilin excretion, the etiological factors concerned in an increase of blood destruction are entirely unknown.

A realization of the possible importance of a specific deficiency as a factor in the development of "von Jaksch" picture has come from recent studies of goat's milk anaemia. As Glanzmann pointed out, in cases of goat's milk anaemia with the "von Jaksch" picture the babies are poorly nourished and have chronic gastro-intestinal disturbances, whereas, in the cases with the ordinary hypochromic anaemia, they are usually well nourished. As mentioned in the section on vitamins, Gyorgy has related the characteristic picture of goat's milk anaemia, which he calls "pernicious," to a deficiency of an unknown substance which he thinks is identical with Castle's "extrinsic factor." Whether the deficiency is in the milk itself or in a failure of absorption is doubtful, but that there is a deficiency which is responsible for the injury to erythropoietic function leading to erythroblastosis, there seems now to be little question. Where there is one deficiency there are likely to be others, evidence for which is to be found in the presence of edema and haemorrhagic tendency so common in

the haemolytic erythroblastic group. Moreover, we find here a possible explanation for the association of the "von Jaksch" picture with rickets that has been so frequently stressed in the past.

The difference between the hypochromic and the hemolytic-erythroblastic anaemias lies then in the presence or absence of various responsible etiological agents. Those leading to iron deficiency or to deficient haemoglobin formation such as prematurity, diet low in iron, ordinary infections, would tend to produce hypochromic anaemia. Except in the case of prematurity severe anaemia of this type develops relatively slowly and is rarely encountered in the first six months of life. Those factors leading to deficient maturation of erythrocytes would tend to produce the "von Jaksch" or haemolytic-erythroblastic type. These factors are constitutional, especially in the very young, severe infections (sepsis and syphilis) and (probably) an undetermined dietary deficiency associated in many cases with gastrointestinal disturbance and evidence of other deficiencies (scurvy and rickets). In any case there may be one or more of these factors present in any combination and diagnosis consists in a determination of the part each plays in the development of the final picture.

### ANAEMIA OF THE NEWBORN PERIOD

Anaemia is not common in the first two or three weeks of life and until recently was hardly recognized as occurring except as an occasional manifestation of syphilis, sepsis or malaria. In the last ten years, however, much interest has been aroused by the increasing number of reports of anaemia, especially the type associated with icterus and erythroblastosis which will be discussed shortly. (Before taking this up, however, it will be necessary to consider briefly the factors that may possibly cause anaemia in the first few weeks.)

#### A FACTORS KNOWN TO CAUSE ANAEMIA IN THE NEWBORN PERIOD

In any large series of determinations of haemoglobin and red cells in the newborn period there may be a number of abnormally low values occurring earlier than the usual time for such minimum levels (36)

There is no sharp line to be drawn between the normal and the abnormal (12, 599), the distinction in the borderline case being largely in the point of view of the investigator. The question in these cases is not whether we should classify them as anaemia of the newborn, but what factors in the mother or baby might have led to such aberrant values.

Although infection must be excluded in every case of anaemia in the first week or two of life, it is implicated in relatively few instances (298, 666). Adelheim's (9) case in which the picture of erythroblastosis of the newborn occurred as a result of intrauterine infection with the spirillae of recurrent fever is the only one of its kind I have been able to find. *Syphilis, sepsis, and malaria* are all capable of causing the picture of erythroblastosis (152, 279, 661, 662), but rarely within the first week and usually a week or two later. *Winckel's disease* (13, 38, 116, 640, 719) is a form of acute haemolytic anaemia occurring in the newborn period with haemoglobinuria and cyanosis. It is generally considered to be due to sepsis, but no specific organism has been described. It has been reported to occur as late as the fifth to sixth week of life (38, 116).

Haemorrhage need be no more than mentioned, for it would only exceptionally pass unrecognized if it were severe enough to be the cause of anaemia. *Syphilis and sepsis* may be associated with severe and often uncontrollable haemorrhage usually not commencing before the end of the first week. *Haemorrhage into the adrenal glands* of unknown cause may occasionally be severe enough to cause anaemia, and might under exceptional circumstances pass unrecognized (232, 506). *Ulcers* arising in the gastro-intestinal tract may be an occasional cause of haemorrhage usually fatal. *Thrombopenic purpura* has been reported a number of times (244, 248, 257, 396, 410, 413, 598, 613, 707). In some of these cases the child has subsequently shown a tendency to bleed. The most common condition in which profuse haemorrhage occurs is the so-called *melaena neonatorum*, the cause of which is at present unknown.

Rare causes of anaemia in the newborn include osteosclerosis, and leukaemia (28, 87, 220, 358, 438, 660, 662, 726).

Congenital haemolytic jaundice has been reported to occur in this period (271). Hampson (269) mentions incidentally having seen several families with congenital haemolytic jaundice in which many

of the infants died shortly after birth with icterus. Sickle cell anaemia and Mediterranean anaemia have not been reported in the newborn period.

The regulation of haemopoiesis in the fetus appears to be quite independent of that of the mother, and recognized disease of the mother rarely is related to anaemia in the baby. Parsons (528) has attempted to relate dietary deficiencies in the mother to anaemia in the infant on the basis of experiments with rats. But in human cases, the instances of anaemia in mother and newborn baby not only rest on sufficient evidence of anaemia in the baby but even if present in a few cases might easily be coincidence. Van Creveld and Heybroek (136) reported an interesting case in which in a first pregnancy the mother suffered from a macrocytic anaemia and gave birth to a normal baby, whereas in the second pregnancy her anaemia was kept in check with liver extract, but the baby was anaemic at birth.

#### B ERYTHROBLASTOSIS FOETALIS (ICTERUS GRAVIS)

The majority of cases of anaemia in the newborn period are dependent on factors of which we are at present ignorant. These cases are being reported with increasing frequency, but with little success in analyzing the mechanism by which they develop, or in determining etiological factors beyond the exclusion of syphilis or sepsis. Since we know too little of their fundamental nature to classify them on this basis, we are forced to group them around certain salient clinical or pathological features with the expectation of a gradual realignment as we learn more about them. The most clear-cut group clinically and pathologically is the so called "erythroblastosis foetalis" which brings together, on the basis of a common pathological picture, Universal Fetal Hydrops, Familial Icterus Gravis, and certain cases of anaemia of the newborn in which there is evidence of increased haemolysis. Clinically, these cases are characterized by (1) *Jaundice*, present at birth or appearing within the first two days of life, (2) *Anaemia*, (3) *Erythroblastosis*, (4) *Familial occurrence* especially of icterus gravis, (5) *Fetal type of blood formation* occurring in the liver, spleen, often the kidneys and sometimes other tissues, (6) *Hydrops* may sometimes replace jaundice in the above characterization, but is of little importance clinically since it is incompatible with life.

*Familial occurrence* A striking fact in the family history of icterus



gravis is that the first child nearly always is spared and in some families others in succession even up to the fourth or fifth pregnancy (152, 166, 236), but that once the condition has occurred it almost invariably continues to occur in all succeeding pregnancies. Undoubtedly many of the so-called "sporadic" cases are examples of the onset of a familial occurrence. Hydrops has rarely been reported alternating with icterus gravis (383, 431, 553). In some families instead of a succession of infants with icterus gravis there may be a succession of abortions or still-births interspersed with an occasional case of icterus gravis or hydrops (139, 385). Hilgenberg reported a family in which all the children by the first husband were normal and all by the second had icterus gravis. This, of course, is suggestive of an hereditary factor, but in view of the order in which the normal and pathological cases occurred is well within the range of coincidence. Hawksley and Lightwood report a case in which evidence of heredity was found in the occurrence of icterus gravis in brothers and sisters of the mother.

*Jaundice* This may vary greatly in intensity but in all the cases belonging to this group it appears at birth or in the first day or two after birth. To judge by the amniotic fluid and the vernix caseosa, jaundice may in some cases develop even before birth. In general the slower the development of the jaundice the better the prognosis. In the cases where the jaundice is milder, anaemia can be more easily recognized, so that such cases have usually been classified as "haemolytic anaemia of the newborn" rather than as icterus gravis. It is probable, however, as Diamond, Blackfan and Baty pointed out in 1931 that such cases belong essentially to the group we are describing. Sometimes one may see a case with characteristic family history in which jaundice and erythroblastosis are minimal in extent (152, 622), only the anaemia being present, or jaundice may be present only following a transfusion (622, 154). Occasionally there may be exacerbations of jaundice after apparent recovery had begun (279).

The urine may contain bilirubin and the Van den Bergh test may give a direct reaction, but as far as one may judge from the reported cases the stools are rarely acholic. The factors influencing the degree of jaundice are not well understood. Increased haemolysis is undoubtedly present, but as has been previously pointed out in-

creased haemolysis by itself does not cause as great a degree of jaundice as is present in the majority of these cases. Moreover the rapidity of the fall in red cells is not related to the severity of the jaundice. Obstruction from thick inspissated bile has been inferred from the finding of "bile thrombi" in the canaliculi of the liver, but this is no more than an inference for which there is no satisfactory evidence.

Changes indicative of beginning cirrhosis were reported by Hawksley and Lightwood in infants dying after several weeks. In the majority of these cases anaemia was not a prominent feature.

*Anaemia* This has usually been found on the first day when blood counts have been made at this time. It reaches its height in general during the third week but in individual cases there are all variations in rapidity of development without relation to the severity of the jaundice or the degree of erythroblastosis. Severe jaundice tends to obscure the presence of anaemia, with the result that its frequency in cases of icterus gravis may not be appreciated unless the blood is examined. Red cell counts are often reduced below a million, the lowest count on record being under 400,000, with recovery (Ducas and Jacquet).

*Erythroblastosis* (152, 279, 342, 542, 599) This may vary considerably in its intensity from case to case like the jaundice which it, in general, parallels. In cases with hydrops or with jaundice developing at or before birth the erythroblastosis may be extreme. It is usually greatest at or shortly after birth, tending then to diminish rapidly. Nucleated red cells may persist, however, sometimes in considerable numbers until permanent recovery takes place. At the time of beginning recovery, there may be a temporary increase in the number of erythroblasts.

As indicated in the first part of the work, erythroblastosis may occur in babies otherwise normal and may last even beyond the first week. There is no sharp line to be drawn between the 'normal' and the 'pathological' as Salomensen (599) has clearly shown, either in the clinical or the pathological picture (279).

*Blood picture* The anaemia is of the *macrocytic-hyperchromic* type characteristic of the haemolytic-erythroblastic group, but it must be remembered that macrocytosis and hyperchromia are normal findings

in the newborn period *Reticulocytes* are present in numbers above those usually found at the same age, but are not commonly increased above 10 or 15 per cent, except at the time of beginning recovery. Ross and Waugh on the other hand found higher reticulocyte counts (up to 60%) in the early period. Other signs of regeneration are usually also present, such as polychromatophilia and sometimes basophilic stippling. The *white cells* are usually increased in number, not infrequently above 50,000 (Buhrman and Sanford reported a white count of 260,000). Leucopenia, on the other hand, has rarely been reported (85, 159). A few myelocytes and occasional myeloblasts are commonly present, but any considerable abnormality of the white cell picture is rare and usually confined to the cases with extreme erythroblastosis. Platelets are sometimes reduced in the group with severe icterus, and in this group there is also frequently present a haemorrhagic tendency, but there seems to be no close relation between thrombopenia and the tendency to bleed. Haemorrhages are usually confined to petechiae or larger subcutaneous purpuric patches, but occasionally profuse bleeding may take place from the umbilicus, the nose, or the gastro-intestinal tract. *Bleeding time* is prolonged in these cases but not the coagulation time.

The *fragility* (152, 279, 585) of the red cells in hypotonic salt solution is sometimes increased, and sometimes diminished, but more often normal.

*Clinical picture* The picture of icterus gravis is too well known to require recapitulation here. In the cases with milder jaundice in which anaemia is more evident there may be little in the clinical picture to attract attention. In the more severe cases the *heart* may be enlarged to percussion and occasionally death may be due to cardiac failure. At autopsy the heart is frequently found to be enlarged. The *spleen* is usually enlarged even on the first day of life. Splenomegaly is, however, rarely more than moderate. Fluctuations in the size may occur, and there may be an increase following a transfusion when the transfused blood is haemolyzed. The spleen returns to normal after recovery but some splenomegaly may persist for several months. The *liver* is also usually increased in size, occasionally reaching the level of the umbilicus. Signs of cerebral involvement are not infrequently present. They should be viewed with some appre-

hension because of the possibility of the development of the so-called "*Kernicterus*" (386, 755, 756), which may lead to permanent cerebral changes—spastic paralysis and mental retardation

**Prognosis** In the cases with severe icterus appearing at birth or shortly after birth the prognosis is bad, the mortality lying somewhere about 70 per cent or higher in untreated cases. On the other hand, in the cases in which the jaundice does not appear until the second day, the prognosis has been good. The severity of the anaemia seems to have little to do with prognosis, and death seldom is the result of the reduction in haemoglobin. The cause of death is not clear in the

TABLE 14

*Data concerning treatment and recovery in anaemia of the new born (icterus gravis cases)*

10 DAY PERIOD UNDER CONSIDERATION	NUMBER OF CASES	TREATED IN PRESENT PERIOD					TREATED IN PREVIOUS PERIOD				UNTREATED IN PRESENT OR PREVIOUS PERIOD			
		Number	Permanent recovery	Partial or temporary recovery	No effect	Died	Number	Permanent recovery	No effect	Died	Number	Permanent recovery	No effect	Died
Birth to 10 days	55	21	1	5	12	3					34	1	22	11
10-20	39	23	8	8	7	0	11	2	9	0	10	4	4	2
20-30	23	8	4	3	0	1	13	5	8	0	4	1	2	1
30-40	11	6	5	1	0	0	2	0	2	0	3	0	3	0
40-50	6	3	2	1	0	0	1	0	1	0	2	1	1	0
50-60	3	2	2	0	0	0	1	0	1	0	1	1	0	0

majority of cases. In a few cases infection may be present, in another small number, cardiac failure, in one or two cases haemorrhage has been sufficiently profuse to be a factor in the fatal outcome. In nearly every fatal case, whether treated or not, death has occurred within the first twelve days. When death has occurred later it has usually been preceded by signs of infection.

**Treatment and recovery** The data concerning treatment and recovery are summarized in table 14. Of twenty-one cases treated in the first ten days of life there was only one in which immediate permanent recovery took place, according to the report, and five partial or temporary recoveries. In the latter group are included (1) Cases in

which transfusions frequently repeated have succeeded in maintaining the red cells and haemoglobin at an adequate level but in which there is reason to believe that the responsible pathological process is still active, (2) Cases in which treatment may have a temporary effect with return of the red cells and haemoglobin toward the former level. The principal difference between the untreated and treated cases in the first ten days of life was in the mortality.<sup>7</sup>

The effect of transfusion in terminating the pathological process is another matter. In the first twenty days twenty-two babies received no treatment, of these five recovered spontaneously to which may be added one more who began his recovery on the twenty-first day, making six in all or 28 per cent. In the same period thirty-three babies received either transfusion or blood intramuscularly at some time. Of these eleven began permanent recovery within the first twenty-one days (33 per cent). Two of these, however, had received their transfusions in the previous period but had not responded to them immediately. This suggests that the pathological process is to a large extent self-limited and that treatment in the first twenty days has little effect in bringing it to an end.

The third point to be mentioned is the temporary effect of transfusion. In many cases, especially in the first twenty days, transfusion has no effect whatever on the level of haemoglobin and red cells (86, 152, 387, 482, 585, 622, 750), in fact in some cases the transfused blood is rapidly enough destroyed to cause increase of jaundice and enlargement of the spleen. In some, however, the immediate effect of transfusion is maintained for a time before the red cells and haemoglobin return to a lower point (86, 152, 279, 622). The duration of this partial response becomes greater as time passes, and in some, permanent recovery begins before another transfusion is given (16, 152, 302, 482), as we may see from the figures in the middle section of the table.

A fourth point is that treatment was always successful in initiating

<sup>7</sup> The reason for the relatively low mortality in the table is (1) That this tabulation includes the more favorable cases in which jaundice appeared on the second day, and (2) that the rapidly fatal cases in which there were no studies during life have not been included. The figures are quite sufficient to indicate the necessity for transfusion in the reduction of mortality.

either permanent or partial recovery after the twentieth day. In two cases iron initiated the recovery (139, 482). These facts suggest that after the original process is at an end, haemopoietic stimulation is necessary just as it is often necessary in post-infectious anaemias, as we have seen in the section on infections. Evidence for such stimulation may be found in a rise in reticulocytes and sometimes in normoblasts following the transfusion or iron administration which initiates permanent recovery.

Lastly, when recovery finally takes place it is permanent and there has not been reported a later tendency to haemolytic or erythroblastic anaemias. Permanent recovery may not, however, take place until after the thirtieth day and in a few cases was delayed until the end of the second month. Occasionally the anaemia changes during recovery to a hypochromic type for which iron is indicated as in the common hypochromic anaemia of infancy.

The question of the efficacy of intramuscular injections of blood is still unsettled, but this procedure should not be relied upon to the exclusion of transfusion the effect of which, on mortality, is undoubted.

*Etiology and pathogenesis* In the condition as it has been described here, we are dealing with a syndrome that is the result of some fault of haematopoiesis. The importance of increased haemolysis is questionable. Undoubtedly it occurs, but there is no satisfactory evidence that it is of primary importance, that is that the erythroblastosis is merely the neonatal response to the need for greatly increased blood regeneration. Even if this were the case, we would still need to explain why the newborn infant reacts with a type of blood formation that is encountered later only under very abnormal conditions. Moreover, recovery from haemorrhage at this period is not attended by any such picture, and as has been already pointed out the erythroblastosis does not parallel the severity of the anaemia. The histological appearance has been compared to that which is present normally in the fourth or fifth month of gestation. This has led to the idea that the chief fault lies in a failure of haemopoiesis to develop beyond this stage. If this were the case one would hardly expect haemopoiesis to reach a normal level within three weeks of extrauterine life after failing to develop in the preceding four or five months unless the failure to develop were due to some defect associated with gestation.

The other alternative is that the condition is due to a retrogression of haemopoiesis to an earlier stage of development analogous to what occurs in pernicious anaemia

Our knowledge is not yet sufficient to permit a discussion of etiology beyond the mere indication of possibilities (1) Infection seems unlikely for it must be one that affects the infant in each succeeding pregnancy and therefore must be present in the mother without causing manifestations Syphilis is, of course, such an infection but syphilis has been excluded in all the reported cases (2) Intoxication is a possibility for which at present there is no evidence It must either be something arising from the fetal side of the placenta or else something to which the mother's tissues are immune while the babies are susceptible (3) Deficiency whether of material or of process must be considered a possibility up to the present virtually untested. To be sure the mother's diet has been considered and usually found adequate, and the mother rarely gives evidence of the presence of a deficiency but the problem of deficiency in the fetus has hardly been touched

In dealing with these possibilities, certain points may be considered (1) The family history in which after a number of normal infants in succession, all succeeding infants are affected, (2) The health of the parents, lack of anaemia in the mother, absence of toxemia, etc Moreover, there is no evidence of any gross deficiency in the diet, or of any condition leading to deficiency, (3) The striking rarity of premature babies among the reported cases, (4) The presence of the condition at birth and its tendency to spontaneous disappearance in the second or third week of life, (5) The permanence of the return to normal after recovery has taken place

In many ways "erythroblastosis foetalis" behaves like a definite disease, but this does not mean that we must look for a single cause for it In a sense it is analogous to cirrhosis of the liver, a pathological picture, into the production of which more than one factor may enter In some it may be a developmental failure in which an hereditary factor may be present In some (probably very rare) there may be infection, as in Adelheim's case of recurrent fever transmitted to the baby in utero, in others, some deficiency or a delay in assuming a normal function may be the factor It is of no assistance to an under-

standing merely to exclude the obvious, and then to group the remaining cases together as a "disease entity" Such a collection of cases is little better than a waste basket

*Diagnosis* The problem of diagnosis is two-fold 1 It is necessary to distinguish cases of icterus gravis with erythroblastosis and anaemia from other cases with severe jaundice Congenital atresia of the bile ducts should rarely cause difficulty, but recently Pasachoff and Wilson (536), and Rupilius (596) have reported cases in which, in addition to congenital atresia, there was also a typical picture of erythroblastosis The association of these two may be more than a coincidence but it is not easy to find a reason for it The one condition that might be difficult to distinguish is severe icterus neonatorum, and this for the reason that there seems to be no real line between icterus gravis with erythroblastosis and anaemia on the one hand, and physiological icterus with the "normal" fall in red cells and haemoglobin and an occasional persistence of nucleated red cells beyond the usual period on the other We can only note that the earlier the icterus appears the more severe it is likely to be and the greater in general is the erythroblastosis, while when the icterus appears after the second day not only is erythroblastosis not present, but anaemia is very unlikely to occur Until we know more of the processes responsible for both conditions we are not prepared to say that they are due to essentially different pathogenesis

2 The second problem of diagnosis is perhaps the more important, for it has to do with the problem of the recognition of the factors responsible for the condition, and an understanding of the process by which it develops If we tend to exclude cases in which the cause has been ascertained, that is merely for convenience in discussion and classification Adelheim's case is no less one of erythroblastosis foetalis because he happened to be successful in determining one of the responsible factors In one article reviewing the cases on record one case was excluded from consideration because the mother had had tuberculosis, if tuberculosis in the mother had nothing to do with the question, there is no reason for the exclusion, if, on the other hand, tuberculosis in the mother was a factor (rather improbable) this is of the utmost importance The reviewer in this case was misled by the term "primary" so often applied to anaemia of the newborn Anaemia



without cause is an absurdity, an elementary fact too often forgotten by those who use the term "primary," and it is waste of time to invent criteria for the sake of applying a name when the purpose of diagnosis is to understand a process

#### C ANAEMIA OF THE NEWBORN WITHOUT ERYTHROBLASTOSIS OR ICTERUS GRAVIS

In the cases included in this group there is an occasional *family history*—not of icterus gravis, but rather of abortions or still-births, or anaemia without jaundice (1, 69, 136, 673) *Erythroblasts* are sometimes present to a slight extent and in a number of cases are increased at the time of beginning recovery (136, 537, 566, 666) The *anaemia* is generally of the macrocytic-hyperchromic variety usual in the newborn period. Evidences of *regeneration*, usually present when looked for were sometimes absent indicating in these cases a hypoplastic process. The rapidity with which the anaemia may sometimes develop suggests the presence of increased haemolysis in spite of the absence of jaundice (11, 273, 531, 566) There is no *haemorrhagic tendency* in any case of this series, and the *platelets* were not found reduced

*Prognosis and fatal cases* Prognosis is in general good, as in the group with relatively mild jaundice and erythroblastosis. In a few cases death occurred in the first ten days of life, but there is evidence to be discussed shortly that these cases differed from the majority

*Treatment and recovery* In untreated cases recovery took place during the fourth and fifth week (69, 70, 136) In the transfused cases recovery generally began in much closer relation to the transfusion and most of the treated cases had begun their permanent recovery by the end of the third week (11, 171, 242) Iron administration was followed by rapid recovery in two cases, previously showing no tendency to recovery (1, 504)

*Etiology and pathogenesis* Stransky (666) divided the anaemias of the newborn into the regenerative and the aregenerative or hypoplastic. Susstrunk considered his own case aregenerative in spite of the tissue erythroblastosis, because the bone marrow was hypoplastic. In Abbot and Abbot's case the femur marrow was hypoplastic while the sternal marrow was hyperplastic and there was erythroblas-

tosis in the liver. The case of Brown, Morrison and Meyer was hypoplastic both clinically and at autopsy, and the same was true of two cases of Passachoff and Wilson (536, 537), the second, one of fetal hydrops. Van Creveld's was also "hypoplastic" on the grounds of the almost complete absence of reticulocytes at the height of the anaemia. Happ (274) considered his second case "hypoplastic." Thus, we are able to separate a group of cases in which hypoplasia, confined to the erythropoietic tissue, is present to some extent. In this group the prognosis is apparently very poor, only one out of the six cases having recovered.

Some of the cases appear to be probably haemolytic in nature even though jaundice is absent, and therefore may be thought of as belonging to the icterus-erythroblastosis group with the difference that the process is less severe, causing only the increased haemolysis and not affecting haemopoiesis. Such cases are those of Pritchard and Smith, Stransky, two cases, Greenthal, Ehrmann, McKay and O'Flynn, Akerren, Noll, Gelston and Sappington, C de Lange.

Still milder are Abbot and Abbot's second case, those of Bonar and of Bonar and Smith from the same family, case 5 of Passachoff and Wilson, case 5 of Parsons, Hawksley and Gittins, and case 1 of McKay and O'Flynn.

Thus, there is a possibility of constructing a continuous series at one end of which is icterus gravis and erythroblastosis of the severest type, with high mortality, and at the other end cases that differ from the normal only in the rapidity of the fall of red cells and haemoglobin.

As has been previously pointed out, the fall in red cells and haemoglobin in the normal baby appears to be due to a combination of two processes—(1) a reduction of erythropoietic activity probably dependent on the fact that the haemoglobin and red cells are at a point above that which is normal for extrauterine life, and, (2) an increase in the rate of haemolysis which varies from case to case but comes to an end usually between about the fifteenth and thirtieth day of life in the full-term and somewhat later in the premature baby. The rapidity of the fall in the red cells and haemoglobin probably depends largely on the haemolytic factor, which is not to be considered normal even though it occurs in the normal baby. The variation in the rate of haemolysis is great even in the normal baby, and it should not be

TABLE 15

*Selected cases of anaemia of the new-born to show the gradual transition from severest to mildest forms*

	JAUNDICE		HAEMORRHAGE	LIVER	SPLEEN	BLOOD					
	Onset	Severity				Day of examination	Red blood cells	Haemoglobin	White blood cells	Erythroblasts	Myelocytes
							mil- lions		thou- sands	thousands	per cent
Buhrman and Sanford	B	++	0	+	±	1	2 9	50	260	210	
Buchan and Comrie	B	++	+	—	+	1	2 7	50	80	147	8
Buchan and Comrie	B	++	0	—	±	7	1 8	55	5 8	1 0	
C de Lange	B	++	+	0	+	2	1 7		53	55	9
						8	3 4	67	15	0 3	
Abt	1st d	++	+	+	++	2	2 5	56	25	100	
Diamond et al, no 8	1st d	++	+	+	++	1	1 8	48	27	61	24
Altitzoglou	1st d	++	+	+	0	1	5 0	90		5 5	
						4	3 5	70		2 4	
Diamond et al, no 1	1st d	++	0	+	+	17	0 65	15	16	1 3	
Andrews and Miller	1st d	+	0	+	+	1	4 8		14	69	4
						4	3 1			2 6	
Andrews and Miller	1st d	+	+	—	—	1	3 6		12 4	6 0	
Altitzoglou	1st d	+	+	0	±	6		57	37	5 0	
						10	2 6	45		4 0	
Diamond et al, no 11	2nd d	+	+	+	+	3	2 1	45		40	
Montfort and Brancato, no 1	2nd d	+	0	0	+	1	1 5	38	27	1 9	
Passachoff and Wilson	2nd d	+	0	+	++	8	1 2	29	25	4 0	
Diamond et al, no 5	2nd d	++	+	+	+	15	1 3	35	16	1 3	
Diamond et al, no 10	2nd d	+	+	++	++	15	0 56	15	49	5 0	
Sanford	2nd d	±	0	++	+	1	2 5	48	68	10 2	
						8	2 9	80	11		
Montfort and Brancato, no 2	2nd d	±	0	0	±	10	1 2	33	39	27	
Montfort and Brancato, no 3	2nd d	±	0	+	0	1	1 7	43	17	1 1	
						14	1 9	41	13	0 13	

TABLE 15—*Concluded*

	JAUNDICE		HAEMORRAGE	LIVER	SPLEEN	BLOOD					
	Onset	Severity				Day of examination	Red blood cells	Haemoglobin	White blood cells	Erythroblasts	Myelocytes
							mil lions		thou sands	thousands	per cent
Ehrman		0	0	+	0	5	1 2	28	20	0 7	2
Gelston and Sappington		±	0	0	±	7	2 3	42	12	0	
Diamond et al		0	0	+	++	17	1 2	28	19	Occas	
Strinsky		0	-	-	-	5	3 6	60	6 2	0	
Pritchard and Smith		±	-	-	+	15	2 4	47	6 8	0	
						10	0 75	10	74	0	
						1	4 4	90	11 6	0	
Bonar and Smith		0	0	0	0	12	2 2	35	14	0	
						24	2 0	40	12	Occas	
						1	4 1	82	14	Occas	2
Abbot and Abbot		0	0	±	+	23	1 6	36	10	0	0
						29	2 3	46	11	0	0

These cases have been selected so as to show as far as possible the extremes of variation in each group. The groups are classified according to the time when jaundice first appeared, and severity of jaundice.

surprising that in some cases sufficient haemolysis may be present to cause anaemia. In the case of Abbot and Abbot and the first case of Bonar and Smith, the sequence of events was similar to what occurs in the normal child but took place in more rapid succession, as if the presence of the anaemia itself had speeded up the development of the opposing process leading to recovery.

When we come to the more severe groups it is impossible to make any such clear comparison with the normal, except in occasional cases. It is probable that we are dealing with two factors, one leading to haemolysis and the other to erythroblastosis and jaundice. It is also probable that bone marrow stimulation may cause the appearance of normoblasts, and even of more immature forms in the circulating blood. There are examples of this in a number of cases at the time of recovery whether spontaneous or induced by transfusion or other therapeutic measures (136, 384, 387, 482, 566, 537, 666). This type

of erythroblastic reaction must not be confused with the erythroblastosis of the newborn, which tends to become greatly reduced in the first ten days of life, and is evidently not due merely to a need for blood replacement

Two facts seem of some significance in relation to the presence of erythroblastosis (1) In almost all the fatal cases of icterus gravis, death took place in the first ten days of life, (2) Transfusion or blood intramuscularly was only rarely followed by permanent recovery, when given in the first ten days, although transfusions repeated every day or two maintained life until recovery began. In the cases without erythroblastosis, however, transfusion was not infrequently followed by immediate and complete recovery when given in this period

The factor leading to haemolysis is present for a longer time, but as long as it is present permanent recovery may not take place. The time at which it disappears completely apparently varies from about the end of the second week to about the end of the fifth week, occasionally later, to judge by the beginning of permanent recovery. The delay in its disappearance would explain the failure or partial effect of transfusions, as has been described earlier. Two facts need to be stressed (1) The absence of jaundice is not incompatible with the presence of increased haemolysis, (2) A slight degree of erythroblastosis may be present during the later period, this is probably dependent on erythropoietic stimulation. Throughout this discussion, I have used the term "factor leading to increased haemolysis" as if it were a positive factor. It may, however, be a deficiency, a temporary failure to supply an antihæmolytic substance on the part of the newborn baby until birth supplied by the mother, an idea first advanced by Hampson

#### D ANAEMIA OCCURRING LATER IN NEWBORN PERIOD

Cases of acute hæmolytic anaemia occurring in the newborn period but beyond the tenth day of life have been reported (39, 185, 269, 531). How to place these cases in relation to other groups is a problem. On the one hand, they may be regarded as examples of "hæmolytic anaemia of the newborn" beginning later than usual, on the other hand, they may be particularly mild examples of that form of

acute haemolytic anaemia known as "Winckel's disease" which is generally considered to be due to sepsis. As a matter of fact in Winckel's disease sepsis has rarely been actually determined, and the belief in this cause goes back to the original description of an epidemic of haemoglobinuria and is strengthened by the fact that the condition has virtually disappeared with the improvement in obstetrical technique. Avoiding any preconceptions, Winckel's disease is merely a form of haemolytic anaemia in which haemolysis is particularly violent, the cause of which is thought to be sepsis. Two cases with haemoglobinuria reported by Bass and Ginandes and by Ferri at 12 and 25 days respectively constitute a possible link between Winckel's disease and those less severe ones without haemoglobinuria which might be classed as acute haemolytic anaemia or as "late" haemolytic anaemia of the newborn.

The problem as in all the cases thus far discussed is not to be solved until we know more of the processes involved and the manner in which they are influenced by etiological factors at present unknown. The best we can do at present is to group them rather loosely according to certain clinical or haematological characteristics for further consideration. The use of dogmatic criteria for diagnosis or the application of a name carries with it the danger of too early a "crystallization" before the nature of the condition is understood.

#### TREATMENT OF ANÆMIA

The problem of treatment is two-fold (1) to save life, and, (2) to influence the process which is responsible for the anaemia. In order to meet this problem we must have an understanding of what is going on and why. Adequate diagnosis is therefore the first requisite of a rational therapy and by diagnosis is meant a clear understanding of the factors responsible for the entire condition of the patient and not merely the ability to name the condition from which the patient is suffering. The anaemia itself is relatively rarely a cause of death, so that we are less often called on merely to raise haemoglobin and red cells, than to direct our therapeutic efforts to the treatment or prevention of the cause, or to the influencing of the pathological process.

when the cause is unknown or cannot be reached. In the section that follows, I shall consider briefly the various therapeutic measures, discussing their possible effect as far as is known and the indications for their use.

#### A TRANSFUSION

The most obvious action of transfusion is to raise the level of red cells and haemoglobin, and its most obvious indication is to relieve a situation that is threatening the life of the patient. The total effect of transfusion, however, far transcends the mere raising of haemoglobin and red cells, so that we are compelled in many instances to infer a direct or indirect action on the process which is responsible for the anaemia. In some cases, especially of nutritional anaemia, the course suggests that the anaemia itself is a factor in the prolongation of the conditions responsible for the pathological process, and that the mere raising of haemoglobin is sufficient to break the vicious circle and restore the normal equilibrium. In such cases anything that will cause a rise in haemoglobin will have the same effect and iron has largely replaced transfusion for this purpose. In others it is probable that the process to which the anaemia is due is itself self-limited and that transfusion merely tides the patient over the critical period until the reparative processes begin. Examples of this may be found in anaemia of the newborn. It is also probable that in some cases of acute haemolytic anaemia the alleged specific effect of transfusion is more apparent than real.

During *infections* it is difficult to raise the haemoglobin by any means other than transfusion. In such cases the effect may be either to improve the condition of the patient so that he is better able to withstand the infection, or actually to supply antibodies. If the infection is not influenced by the transfusion the haemoglobin quickly returns to its former level. Transfusion is particularly indicated in cases of severe anaemia in which pneumonia develops (191). Ordinarily, however, in pneumonia the moderate degree of anaemia often present does not necessitate transfusion, though the procedure may be of great benefit to the patient in helping him combat the infection.

In the haemolytic-erythroblastic group, the effect of transfusion is quite obscure. In the constitutional group represented by congeni-

tal haemolytic jaundice, sickle cell anaemia, and Mediterranean anaemia, transfusion may have no more than a temporary effect given in quiescent periods. During crises, however, the rise in haemoglobin following transfusion is often as dramatic as it is in acute haemolytic anaemia but one is just as often left wondering whether the effect of transfusion is not more apparent than real. Sometimes, however, one may see a result that definitely points to an influence of transfusion on the pathological process itself, though such an influence is never more than temporary. A study of urobilin excretion in these cases has indicated that transfusion is followed by a temporary diminution in the rate of blood destruction (unpublished). It is therefore possible that transfusion may act in these cases by supplying something that was lacking in the patient. In the non-congenital types, (120, 514), the efficacy of transfusion depends on the continuance or disappearance of the responsible factors. In this group transfusion is superior to iron in treatment, but favorable experience with liver indicates that transfusion may not be a necessity, though, as in the case of hypochromic anaemia, it may be indicated where speed is desired.

In the hypoplastic-aplastic group, transfusion in general has no more than a temporary action and rarely influences the eventual outcome. There have, however, been a few cases in which persistence in transfusing has been followed by recovery. There is, of course, always the possibility that if the patient is kept alive long enough he may eventually be able to correct the disturbance that is responsible for the failure to establish a normal equilibrium.

The dangers of transfusion have been exaggerated. The most serious danger is from the use of mis-matched blood, leading to excessive haemolysis haemoglobinuria, kidney damage and sometimes death. A second obvious danger is the transmission of syphilis or malaria. A third danger encountered with great rarity is anaphylactic shock or other types of allergic reaction usually after repeated transfusions from the same donor (84, 213, 261, 730). Cardiac failure during transfusion has been reported.

In some cases, even when matching is satisfactory the transfused blood is haemolyzed (44, 229, 730). This happens particularly in severe haemolytic anaemias. It is apt to be forgotten that in such



cases the rate of haemolysis is such that the patient destroys more of his own blood in a day than can be replaced by transfusion so that it is not surprising that the transfused blood may be destroyed in addition. It is perhaps more a matter of remark that the transfused blood is not more often destroyed. No harm usually results from such a destruction of transfused blood and it merely indicates that the haemolytic process is still active. Occasionally excessive haemolysis involves not only the donor's blood but also that of the recipient as in a mis-matched transfusion (472, 515). Under such circumstances transfusion is naturally contra-indicated.

In aplastic anaemia, leukaemia and some other conditions involving haemopoiesis, unfavorable reactions to transfusion often become more frequent and severe as the disease progresses. Under such conditions it may be better to stop this form of treatment and allow the patient to die in peace. The common febrile reactions occurring after transfusion often with chill and temporary rise in temperature are of no importance and may be disregarded.

Intraperitoneal transfusions may be used in place of intravenous, in most cases the blood being rapidly absorbed into the circulation (467, 521, 593). In very sick children, however, absorption is greatly retarded so that this route should be avoided in such cases (113, 192, 432).

Injections of whole blood or serum may sometimes be used in place of transfusions where immediate increase in red cells and haemoglobin is unnecessary. The results in general are less satisfactory, but the procedure may be valuable during the preparation for transfusion especially in acute haemolytic anaemia or haemorrhagic disease. Intramuscular injections of blood should, however, not be relied on to the exclusion of transfusion when the condition of the patient is precarious. Good results have been reported from the use of frequent injections of blood in "von Jaksch anaemia" (47, 189).

#### B IRON AND COPPER

The value of iron in the treatment of hypochromic anaemia is now so generally recognized that there is nothing to be gained by presenting the evidence on which iron therapy rests. Most of the work at present is concerned with (1) The form in which iron is best given, (2)

Physiological action, (3) Limitations of iron therapy, (4) Methods of enhancing its action

(1) *Iron should be given in inorganic form* The old dictum that one should buy iron in the market and not in the apothecary shop should be abandoned as far as it concerns the treatment of anaemia. The maximum effects of iron are obtained by flooding the body with a large excess of easily available iron, and food does not contain sufficient iron to achieve this result, or the iron of the food is not easily enough available. Iron should preferably be given in soluble form, so that its availability should not have to depend on the gastric acidity which may be deficient in infants. Recent work indicates that ferrous iron is of greater value than ferric and may exert its maximum effect with a smaller dosage. The greater value of ferrous iron has not yet been demonstrated in anaemia in infancy. It is not enough merely to treat two series of infants and compare rates of recovery statistically, it must be shown that a maximum effect may be obtained by a smaller dose.

(2) *The physiological effect of iron is two-fold* It stimulates haemopoietic activity and it supplies a material essential to the formation of haemoglobin. The effect of iron in curing a hypochromic anaemia has been an important support for the opinion that hypochromic anaemia was essentially due to iron deficiency. As has been pointed out in the section on iron metabolism, we must define iron deficiency in terms of availability of iron, for except under extreme conditions there is no evidence that the body is deficient in iron that might be made available if we knew how. This is particularly true after an infection when the failure of the haemoglobin to rise except after the administration of iron cannot be ascribed to deficiency. Whether its effect is in stimulation, or in supplying iron in an available form we have at present no means of knowing. From the point of view of the clinic and the therapeutic use of iron the question of physiological action is probably academic, but there is at present a tendency to speak of iron deficiency anaemia without a clear realization of exactly what is meant.

(3) *Limitations of iron therapy* Iron will have no effect if haemopoietic tissue is not stimulated. Such a condition is present in the first six weeks of life while the haemoglobin and red cells are still

falling As already stated this is probably not due to an abnormal condition of the bone marrow, but merely that one ordinarily does not expect to raise the haemoglobin or red cells that are above the point that is normal for the conditions that exist at that time During severe infections iron has little or no effect and during mild infections iron has a somewhat diminished action In the hypoplastic-aplastic group it has no effect In fact a failure to react to iron with reticulocyte rise in the presence of anaemia may be used as evidence of the presence of a factor of "hypoplasia" in the pathogenesis of the anaemia

In the haemolytic-erythroblastic group iron has a limited application It will of course have no effect on constitutional factors so that one need not expect any reaction to iron in cases dependent on such a factor except in so far as there may be iron deficiency in addition In those dependent primarily on extrinsic factors, the so-called "von Jaksch" anaemia there may be some cases that will respond well to iron, while in others the result will be no more than partial

(4) *Measures to increase the efficacy of iron* The value of hydrochloric acid has not yet been settled It appears logical to use it, especially if there is hypo- or achlor-hydria and insoluble iron preparations are used With the use of soluble preparations, it seems a priori superfluous No clinical studies have yet been reported to settle this point

The value of copper has already been briefly discussed Its action appears to be limited to cases receiving medicinal iron at the same time, and consists in aiding the formation of haemoglobin, probably as a catalyst (90, 313, 314, 406, 529, 695) Its action is best seen in those cases in which iron alone has failed to cause a complete return to normal Copper is rarely necessary for complete recovery but may be useful in accelerating recovery

#### C LIVER THERAPY

The indications and limitations of liver therapy have not yet been adequately settled The older statements that liver had no effect on the anaemia of infancy have had to be revised, but we do not yet know whether or not liver supplies anything that cannot be supplied by other means Its most useful application is in the treatment of cases belonging to the haemolytic erythroblastic group in which the

predominant factors are other than constitutional, especially the type with high color index and tendency to "hypoplasia" often called "pernicious" (271, 289, 538, 418, 696, 175) The mode of action is unknown in most cases In some, it seems to have a non-specific stimulating effect similar to that of iron, as in the premature baby (318, 454, 330) In others it may supply a more specific type of substance As has been stated previously many of the cases in the haemolytic-erythroblastic group probably depend on a deficiency of some nutrition factor similar if not identical with Castle's "extrinsic factor" The value of liver in this group may be due to the fact that it supplies this factor Benjamin's<sup>6</sup> case of "pernicious anaemia" in an infant apparently depends on a deficiency due to a difficulty in absorption, for it was only when liver was given parenterally that the blood picture improved This case had most of the characteristics of pernicious anaemia, but the absence of the "intrinsic factor" was not demonstrated

#### D SPLENECTOMY

The value of splenectomy is limited The most outstanding results are obtained in the haemolytic-erythroblastic group, more particularly in congenital haemolytic jaundice in which there is, clinically at least, a cure in the great majority In the other constitutional types the results are not so clear The consensus of opinion appears to be that it is of value in sickle cell anaemia since the frequency and severity of the crises appears often to be diminished (379, 543) On the other hand, as the child grows older crises tend usually to become less severe spontaneously, so that splenectomy might well be reserved for those cases in which life appears to be endangered by severity of the crises—a small minority In the erythroblastic types, splenectomy is of very doubtful value although in some cases, the patient appears to be temporarily benefited In some of the rare cases of constitutional origin that do not fit into any of the three recognized groups, splenectomy has apparently been of value but in others, death may actually be hastened In general, in infancy and in the types with erythroblastosis splenectomy is rarely indicated

<sup>6</sup> To be published Preliminary report at the 1935 meeting of the Society for Pediatric Research

In the cases in which the predominant factor is not constitutional, splenectomy is of very doubtful value. As indicated previously, prognosis is relatively good in those in which severe infection is not the cause, but a few cases have been reported in which splenectomy has succeeded after other measures have failed (24, 33, 543)

Other conditions for which the spleen is removed—thrombocytopenic purpura, splenic vein thrombosis, cirrhosis of the liver, Gaucher's disease—have only an indirect bearing on the subject of anaemia of infancy. In many cases removal of the spleen materially improves the condition of the blood, even though the disease itself is not fundamentally altered by this procedure. The improvement in blood picture indicates an influence of the spleen on the regulation of blood formation, discussion of which is beyond the scope of this article.

#### E DIETARY TREATMENT

Czerny was one of the first to recognize the importance of diet in the treatment of anaemia, but with the passage of time it is becoming evident that the *a priori* reasons he gave for the use of his diet were wrong. The hypothesis of the injurious effect of fat has not one shred of evidence to support it except its plausibility but it has nevertheless found wide acceptance and even now it still appears as the basis for discussions of anaemia in the German literature. As Aron pointed out in 1922 the diet used—limitation of milk and increase in other foodstuffs, especially vegetables—was especially rich in “accessory factors,” to which he ascribed a predominant importance that later work has only partially confirmed. At the present time, with the improvement in infant feeding it is not necessary to stress the importance or the meaning of an adequate diet.

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## THE INFLUENZAS OF SWINE AND MAN<sup>1</sup>

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In the late summer or early autumn of 1918 a new epizootic disease appeared among swine in the middle west. The exact date or locality of its first occurrence remains unknown but careful observers state that cases were seen as early as August on farms in western Illinois. It is certain that the disease caused serious losses among swine on exhibition at the National Swine Breeders' show held in Cedar Rapids, Iowa, from September 30th to October 5th. At the conclusion of the show, the swine, many of them ill, were returned to their home farms and, within two or three days, this new disease was stated to be rampant in the portion of the drove that had remained at home. Shortly thereafter it became widespread among swine herds in Iowa and other parts of the middle west. The epizootic persisted in various localities until January of 1919 and reappeared in the autumn and winter of that year as extensive and severe as in 1918. It has recurred each year but varies annually in its severity and extent.

According to Dorset, McBryde and Niles (1), Dr. J. S. Koen, an Inspector in the Division of Hog Cholera Control of the Bureau of Animal Industry, was the first to recognize the disease as being different from any previously encountered. He was so much impressed by the coincident<sup>1</sup> prevalence of human influenza and by the resemblance of the symptoms seen in man to those occurring at the time in hogs that he became convinced that the two were actually the same. He therefore gave the name of "flu" to this new disease of hogs. The opinion of Koen that "flu" represented an entirely new swine epizootic disease, and that swine might have been infected in the first instance from man, was shared by some veterinary practitioners and many farmers in the middle west (2). Furthermore, the name "flu," prefixed by the word "hog" or "swine" proved a generally accepted design-

<sup>1</sup> Harvey Lecture delivered March 19, 1936

nation for the condition Since the disease has entered the period of scientific investigation, it has been dignified by the name "swine influenza "

#### CLINICAL FEATURES OF SWINE INFLUENZA

Swine influenza is essentially a disease of autumn and early winter occurring annually among hogs in the middle western states Its onset is sudden and the morbidity rate in an affected herd high, practically all of the animals under one year of age become sick Fever, anorexia, prostration of an extreme type, cough, and a rapid peculiar abdominal type of respiration are salient features of the disease The animals cry out when handled, which has been interpreted as evidence of muscular tenderness A leucopenia is usually to be observed (3) The period of illness is short, varying from 2 to 6 days, and in uncomplicated cases recovery is almost as sudden as the onset The mortality usually ranges from 1 to 4 per cent, but may be higher

#### EXPERIMENTAL TRANSMISSION

Swine can be readily infected experimentally by intranasal inoculation with suspensions of diseased lung or bronchial exudate (3 and 4) The disease is also highly communicable, transmitting with ease by pen contact Experimentally produced swine influenza is clinically similar in all respects to that observed occurring naturally in the field Its incubation period is short, from 2 to 7 days for animals infected by pen contact, and from 24 to 48 hours for animals infected by intranasal instillation Death may ensue on from the 3rd to the 6th day of illness, or later It is preceded by an exaggeration of all respiratory symptoms, an increase in the prostration, the onset of an active, incoordinated delirium, and a progressively intensifying cyanosis The mortality rate for experimental swine influenza is something under 10 per cent

#### PATHOLOGY

Swine naturally or experimentally infected with swine influenza, and killed on from the 3rd to the 5th day of illness, show a similar picture at autopsy The cervical and bronchial lymph nodes are swollen and edematous The trachea contains a white, glassy, tenacious

mucous exudate in from moderate to copious amounts. There is more exudate in the large bronchi, and in the smaller bronchi and bronchioles it completely fills the lumen. In the bronchioles it is of firmer consistency than higher in the respiratory tract and can frequently be

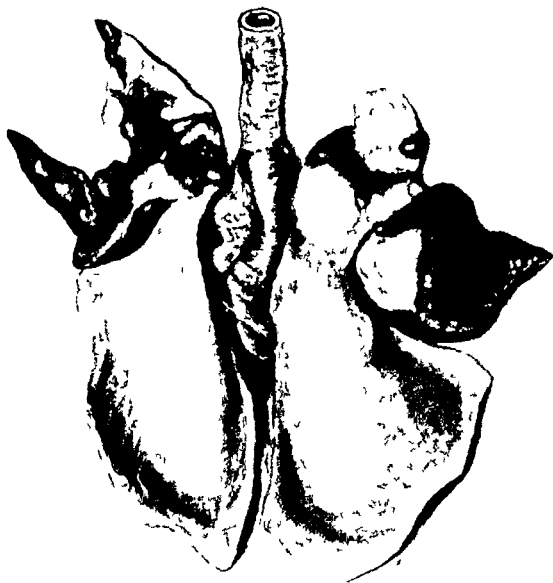


FIG. 1. DORSAL ASPECT OF LUNG IN EXPERIMENTAL SWINE INFLUENZA TO SHOW THE TYPICAL APPEARANCE AND DISTRIBUTION OF THE ATELECTATIC PNEUMONIA.

The lymph nodes at the hilum are swollen and edematous. The sharp demarcation of the pulmonary lesions is noteworthy. Animal chloroformed on the 4th day of illness.

removed in small, white, semitranslucent, sago like masses. The pleurae are usually free of excess fluid or fibrin. The lungs present very constant and characteristic gross changes as depicted in figures 1 and 2. The involved part is purplish red in color, depressed, firm and

"leathery," does not crepitate, and is friable in contrast to its usual rubber-like consistency. The cut surface is moist and the small bronchi exude a thick, glassy, white mucous exudate. The gross picture is that of an atelectatic pneumonia, variable both in amount and distribution, but limited usually to portions of the apical, cardiac and

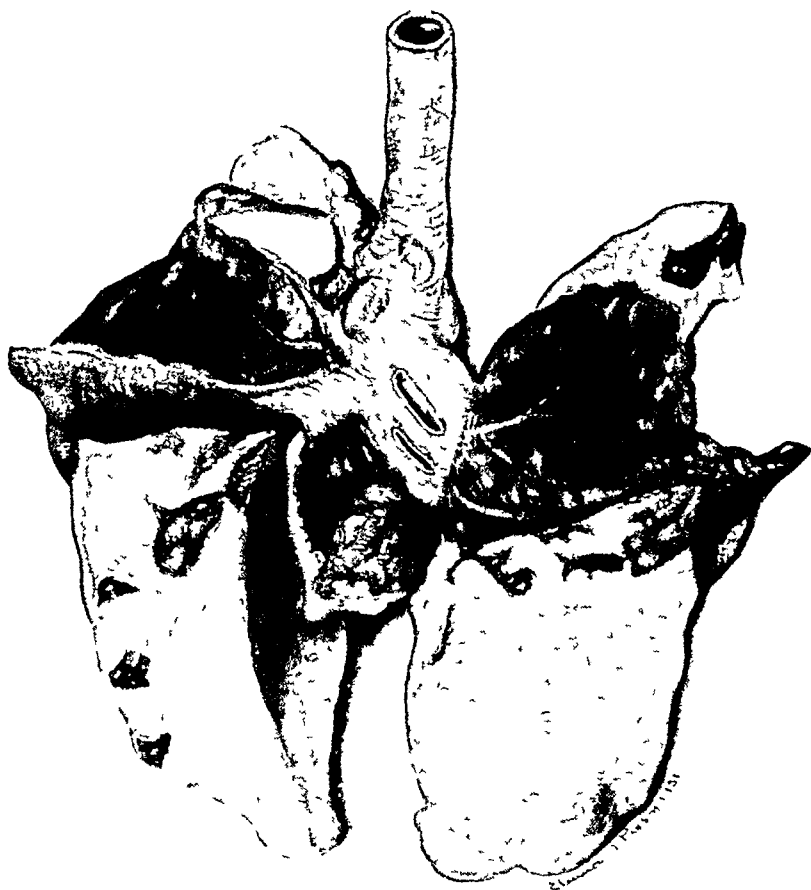


FIG 2 VENTRAL ASPECT OF SAME LUNG

azygos lobes and not infrequently involving all five of these. The adjoining lung tissue is emphysematous, exaggerating the depressed appearance of the pneumonic areas.

In fatal cases the postmortem picture is somewhat different. There is often a sero-sanguineous pleural exudate which sometimes contains

fibrin. The lungs are voluminous, heavy, and mottled purplish-red in color. Only the apical, azygous, or cardiac lobes are consolidated. Thus the true pneumonia is limited to the same portions of lung involved in non-fatal cases. The diaphragmatic lobes, which in swine



FIG. 3. SECTION FROM THE LUNG IN EXPERIMENTAL SWINE INFLUENZA SHOWING DENSE LEUCOCYTIC INFLUX IN SMALL BRONCHI, PERIBRONCHIAL ROUND CELL INFILTRATION AND SURROUNDING ATELECTASIS AND INTERSTITIAL PNEUMONIA. Animal chloroformed on 5th day following inoculation. Eosin-methylene blue.  $\times 75$ .

comprise well over half the actual lung substance, exhibit a hemorrhagic type of pulmonary edema which is in most instances extreme. The markings of the interlobular septa are widened by fluid and the lobes, as a whole, have a glistening swollen appearance. When they are cut across there is an outpouring of a frothy, bloody fluid.



Outside the respiratory tract pathological alterations are variable and probably not of great significance. The spleen is sometimes moderately swollen, the mesenteric lymph nodes are usually edematous, the gastric mucosa is frequently hyperemic, and the stomach empty except for thin, bile-tinged mucus. The mucosa of the colon

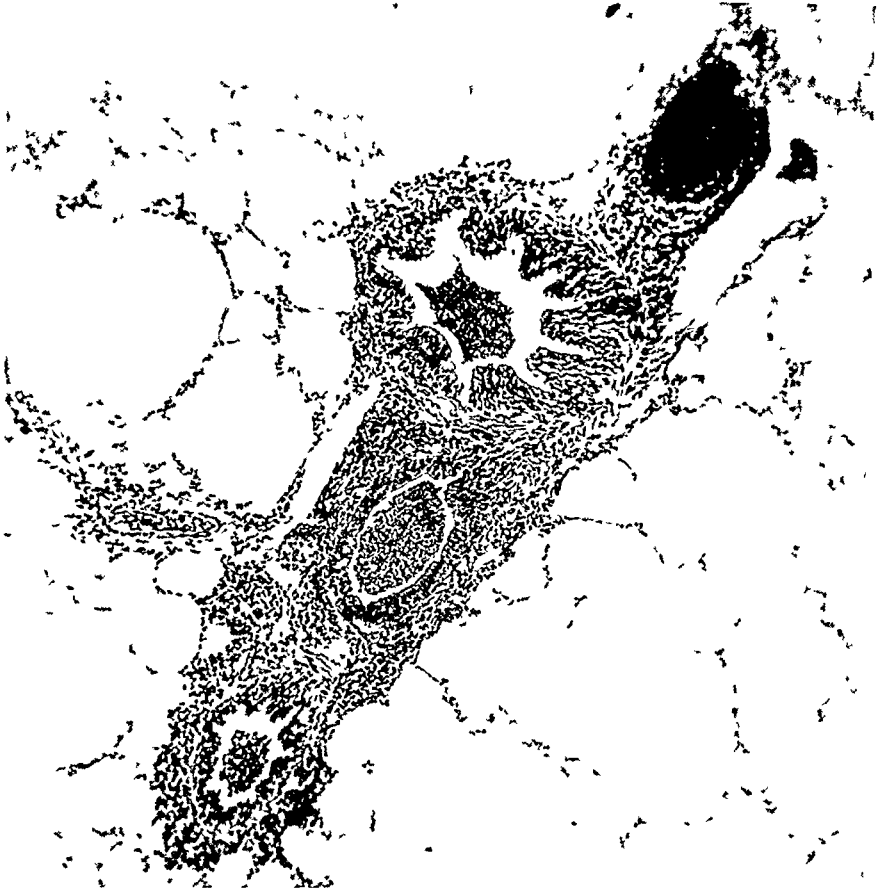


FIG. 4. SECTION OF LUNG FROM A SPONTANEOUS FIELD CASE OF SWINE INFLUENZA SHOWING A BRONCHUS IN AN AREA OF COMPENSATORY EMPHYSEMA TO ILLUSTRATE BETTER THE DENSE PERIBRONCHIAL ROUND CELL INFILTRATION.

The lumen of the bronchus is packed with leucocytes. Animal stunned and bled to death. Eosin-methylene blue.  $\times 75$ .

often exhibits mildly edematous hyperemic patches overlain by a scant catarrhal exudate.

*Histopathology.* The histological alterations in the respiratory tracts of swine sacrificed on from the 3rd to 5th day of illness may be briefly described as follows:

Tracheal sections show little that appears abnormal

Lung sections cut in such a way as to include small bronchi and bronchioles, exhibit the following features. The small bronchi and bronchioles are filled with a polymorphonuclear leucocytic exudate

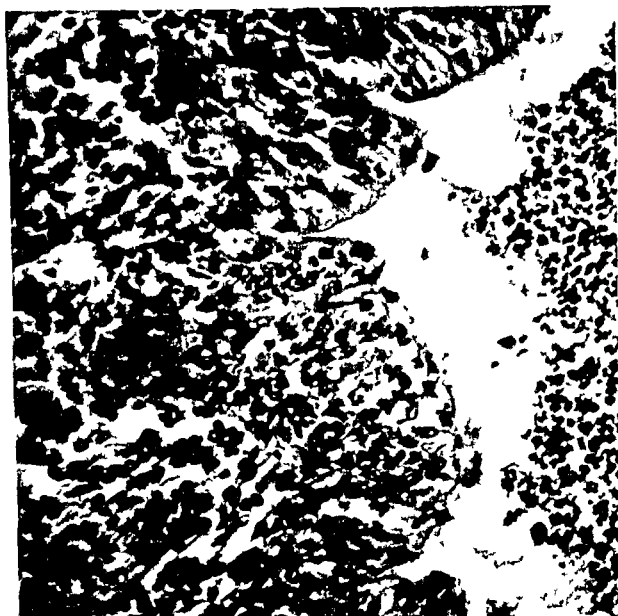


FIG. 5. SECTION OF A SMALL BRONCHUS IN EXPERIMENTAL SWINE INFLUENZA SHOWING LEUCOCYTIC BRONCHIAL EXUDATE, FRAGMENTED AND VACUOLATED EPITHELIUM, DENUDING OF CILIA AND ROUND CELL INFILTRATION OF THE SUBMUCOSA.

Leucocytes have invaded the mucosa. Animal chloroformed on the 5th day following inoculation. Iosin methylene blue.  $\times 450$

(figs 3 and 4). Bacteria are never numerous in this exudate and frequently they are not demonstrable. The cilia lining the smaller bronchi are either entirely gone or badly matted together. The lining epithelium is fragmented, in places partially desquamated, and the cytoplasm of many of the cells appears vacuolated (fig 5). In the

spaces created by the fragmentation of the lining epithelium, leucocytes, singly or in clumps, are sometimes seen. There is an extensive peribronchial round cell infiltration (figs 3 and 4). The areas of lung involvement are of lobular distribution and sharply demarcated from

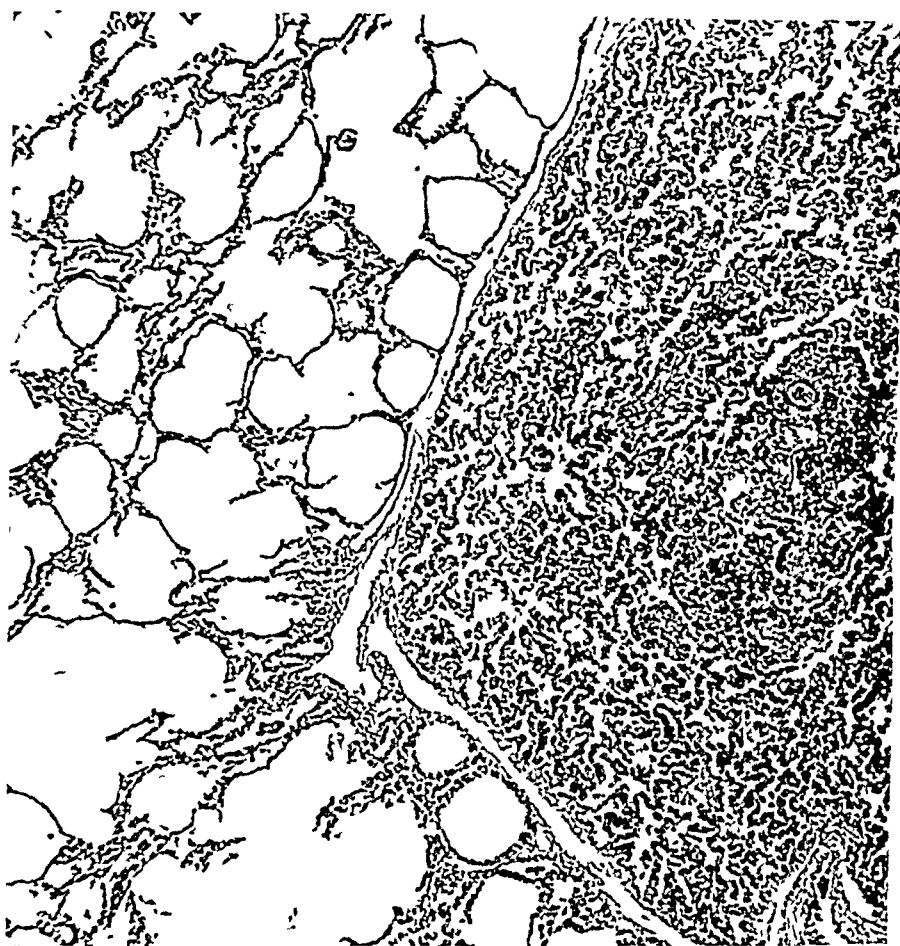


FIG. 6. SECTION OF LUNG FROM A SPONTANEOUS FIELD CASE OF SWINE INFLUENZA SHOWING ATELECTASIS WITH ROUND CELL INFILTRATION OF THE ALVEOLAR WALLS, SCANT LLUCOCYTIC EXUDATE IN SOME OF THE COLLAPSED ALVEOLI, AND COMPENSATORY EMPHYSEMA.

Animal stunned and bled to death. Eosin-methylene blue  $\times 75$

adjacent uninvolved lung by interlobular septa, although a number of adjacent lobules may be, and usually are, affected. In these areas the alveoli are collapsed and frequently contain desquamated epithelial cells, small numbers of mononuclear cells and occasionally some coagu-

lated plasma (figs 3 and 6). Large, feebly stained cells exhibiting a "foamy" cytoplasm are especially numerous in some sections. Leucocytes and red cells are not numerous in the alveoli although it is difficult to find sections, even from very early cases, in which the alveoli

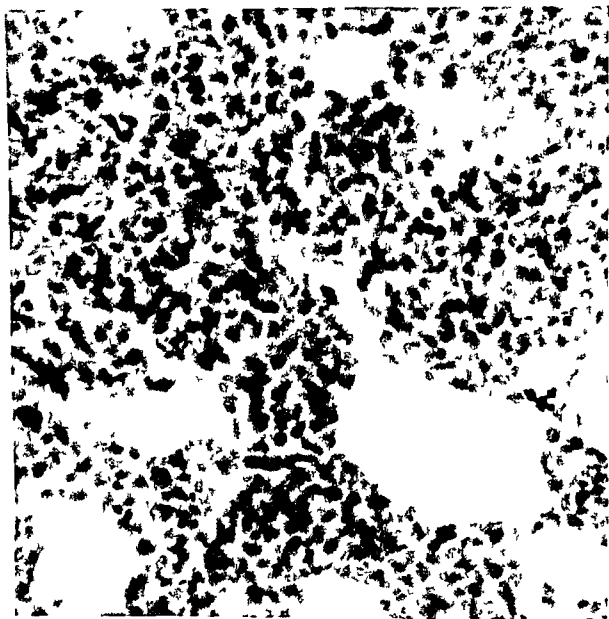


FIG 7 SECTION OF LUNG IN EXPERIMENTAL SWINE INFLUENZA SHOWING ROUND CELL INFILTRATION OF ALVEOLAR WALLS IN AN AREA OF ATELECTASIS

Animal chloroformed on 3rd day following inoculation. Eosin methylene blue  $\times 435$

in some areas do not contain accumulations of them. When present, leucocytes are most abundant in the alveoli opening directly into the terminal bronchioles. The alveolar walls are wrinkled, thickened, and infiltrated with mononuclear cells (fig 7). Dilated capillaries in the alveolar walls are packed with red blood cells, and widened

lymph channels in the interlobular septa are filled with coagulated lymph and small numbers of cells

Histological examination of lung sections from fatal cases reveals a picture similar to that described for non-fatal cases but modified by the presence of an intense edema and congestion

#### ETIOLOGY OF SWINE INFLUENZA

In view of the economic importance of swine influenza, it had been surprisingly little investigated at the time Dr Paul Lewis and I began our studies. Several organisms had been suspected as responsible (4, 5, and 6) but the results obtained in attempting to infect swine with them were not convincing. In addition to the confusion regarding its etiology, the opinions of veterinarians and farmers in the middle west that the disease represented pandemic human influenza surviving as an infection of swine made the problem one of broad interest, since it seemed possible that anything we learned concerning the etiology of swine influenza might later prove applicable to the human disease.

*A hemoglobinophilic bacterium in swine influenza* Our studies were begun in November of 1928. Infectious material in the form of bronchial exudate and pneumonic lung was obtained from swine in eastern Iowa where an epizootic of swine influenza was then in progress. Two strains of the disease were established in our experimental swine and maintained by serial passage at 4- or 5-day intervals. The respiratory tracts of all experimental animals were studied bacteriologically at autopsy. An organism similar to Pfeiffer's *H influenzae* was obtained in pure culture from both first passage swine inoculated with each of the strains. The same bacterium was isolated thereafter from all swine infected in later passages, with either strain of the disease, provided they came to autopsy within 7 days following the onset of fever. Frequently no organism other than this influenza-like bacillus could be recovered from the lungs or the bronchial exudate of infected animals. Here then in swine influenza was an organism like that believed by many to be responsible for influenza in man. The problem of determining the etiology of swine influenza seemed absurdly simple in the beginning for while the bacillus, which we named *Hemophilus influenzae suis* (7), was not easy to cultivate, it could always be isolated from cases of the experimental disease by

appropriate methods. The very difficulties encountered in its isolation and its fastidious requirements of particular media upon which it could be grown seemed to emphasize its importance. In addition, there were numerous cases in which it was the only organism that could be isolated, in these there was no choice but to consider it of etiological importance, unless we wished entirely to deny it a rôle in the disease.

It was, of course, obvious that if the organism were actually the cause of swine influenza it should fulfill Koch's postulates. The first pig inoculated intranasally with what we believed to be a pure culture became ill. The lesions produced were similar to those of swine influenza, and the organism was recovered in pure culture from the respiratory tract. The problem seemed simpler than ever and we were by now convinced that *H influenzae suis* was the agent responsible.

When we repeated the experiment in a second pig, however, we failed to obtain an infection. The animal remained perfectly normal and no lesions suggestive of influenza were to be seen when it was killed after a period of observation. Four other pigs inoculated intranasally with pure cultures of the organism likewise remained normal and we began to doubt the first experiment and the correctness of the view that *H influenzae suis* caused swine influenza. Even now, there is no certain explanation of that first positive experiment, provided indeed the animal actually had influenza as was believed at the time.

Since the first experiment was performed with a culture that had been transferred only four times on artificial media, we considered for awhile the possibility that we were dealing with a bacterium that very rapidly lost its virulence under cultivation and tried various means to restore its hypothetical pathogenicity. These were unsuccessful and, because our strains of the disease maintained by continuous serial passage in swine were finally lost, work for the year was discontinued.

The following year the swine influenza epizootic in Iowa was less severe and extensive than that of 1928. Four strains of infectious material were obtained and transmitted to our experimental swine. Again *H influenzae suis* was regularly encountered in animals ill of the experimental disease. In addition, the organism was cultivated from six field cases in 5 different herds. Freshly isolated pure cultures were again found harmless for swine of proven susceptibility. The

1929 strains of the disease could not be maintained for long by serial passage and only about one month's work was possible

In 1930 two new strains of swine influenza were obtained in Iowa. These proved readily transmissible and again *H influenzae suis* was the predominant or only organism that could be cultivated, but all efforts to produce the disease with these new cultures were unsuccessful.

*A filtrable virus in swine influenza* A few attempts to infect swine by administering bacteriologically sterile Berkefeld filtrates of known infectious material intranasally had been made during the first year's work. No illness remotely resembling swine influenza had resulted and the experiments were considered negative. By 1930 when *H influenzae suis* had failed so miserably to fulfill the requirements of an etiological agent, we were again ready to consider the question of a virus etiology in swine influenza.

Swine were inoculated intranasally with Berkefeld V or N filtrates of known infectious lung and bronchial exudate suspensions and autopsied in 4 or 5 days. Of 10 experiments, 3 were interpreted as negative, while in the remaining 7 some evidence was obtained that the injected filtrate had contained an infectious agent. The illness induced by this filtrable agent, however, was definitely not swine influenza and will be referred to hereafter as "filtrate disease" (8).

Clinically the filtrate disease is much milder than swine influenza. Sometimes it is so ill-defined that infections are difficult to recognize. In most cases there is no elevation of temperature, while in a few a fever for one day is observed. This is at marked variance with the 4 to 6-day fevers seen in typical swine influenza. The usual symptoms shown by filtrate-inoculated swine are a moderate and transient apathy, some diminution in appetite for a period not exceeding 3 days, occasionally a slight cough, and, as in swine influenza, a moderate or marked leucopenia. The extreme prostration so common in swine influenza is not seen.

The lesions are slight as compared with the 4 and 5-lobe pneumonias of swine influenza. The lungs show only a scant, scattered, patchy, lobular atelectasis involving as a rule not more than small portions of 1 or 2 lobes.

Histologically the bronchial epithelium is found to be damaged, there is a heavy peribronchial cuffing with round cells and the alveolar

walls are wrinkled, thickened and infiltrated by round cells. The collapsed alveoli are usually free of cells and, in contrast to swine influenza, no leucocytes are present, as a rule, in the lumen of bronchi or in the alveoli of involved areas of lung.

The filtrate disease proved transmissible in series and passage did not modify its character, thus indicating that its mild nature had not been due to dilution of the inciting agent during filtration. Furthermore, it proved highly contagious.

The filtration experiments indicated that infectious material from experimental cases of swine influenza contained an agent capable of passage through Berkefeld V or N filters and possessing slight but definite pathogenic properties for swine when administered intranasally. Subsequent investigation has shown that this agent possesses all the properties requisite for its classification as a filtrable virus (8).

*H. influenzae suis*, while constantly encountered in cultures from animals with typical influenza, was not present in those suffering the filtrate disease, not infrequently their respiratory tracts proved bacteriologically sterile.

Following the establishment of the presence of a filtrable virus in swine influenza, the situation, as to the etiology of the disease itself, became even more confused than it had been when *H. influenzae suis* was suspected. Here, instead of one agent that could be looked upon as of possible etiological importance, were two such agents. The organism could not be completely ignored, for, while it was apparently perfectly harmless for swine, its constant presence in so many samples of infectious material from the field and its persistence on serial passage through experimental swine kept attention focused upon it. Neither could the filtrable virus be accepted whole-heartedly as the cause of the disease because, while it unquestionably possessed pathogenic properties for swine, the mild illness that it caused was certainly not swine influenza. The dilemma was perplexing. Considered in the light of views current that an infectious disease was caused by a single agent, we had reached the point in our experiments where it appeared that we had one too many under suspicion. For awhile it seemed essential to choose between the two. It may be pointed out that this situation was not unique to our problem. For years, investi-



*Effect of inoculating swine*

EXPERIMENT NUMBER	INFECTIOUS MATERIAL FROM SWINE, NUMBER	SWINE INOCULATED, NUMBER	INOCULATED INTRANASALLY WITH	
1	860	859	10 cc Berkefeld N filtrate	M
	Strain 14 (1930)	861	8 cc Berkefeld N filtrate + 2 cc culture HIS*	T
	In infusion broth	871	10 cc unfiltered suspension	T
2	872	875	4 cc Berkefeld N filtrate	M
	Strain 15 (1930)	874	4 cc Berkefeld N filtrate + 2.5 cc culture HIS	T
	In infusion broth	873	2.5 cc culture HIS in 4 cc infusion broth	N
		876	4 cc unfiltered suspension	T
3	878	894	7 cc Berkefeld N filtrate + 2 cc sterile horse blood	M
	Strain 15 (1930)	897	Infected by contact with Swine 894	M
	In distilled water	892	7 cc Berkefeld N filtrate + 2 cc culture HIS	Ty
		896	Infected by contact with Swine 892	Ve
		893	2 cc culture HIS in 7 cc distilled water	No
		895	5 cc unfiltered suspension mixed with 10 cc normal swine serum	Ty
4	907	911	4 cc Berkefeld N filtrate	M
	Strain 15 (1930)	910	4 cc Berkefeld N filtrate + 2 cc culture HIS	M
	In infusion broth	915	Infected by contact with Swine 910	M
		912	2 cc culture HIS in 4 cc infusion broth	N
		913	4 cc unfiltered suspension	M
5	918	919	8 cc Berkefeld N filtrate †	M
	Strain 15 (1930)	920	8 cc Berkefeld N filtrate	M
	In infusion broth	921	8 cc Berkefeld N filtrate	M
		923	8 cc Berkefeld N filtrate + 2 cc culture HIS	Ty
		922	2 cc culture HIS in 8 cc infusion broth	No
		951	8 cc unfiltered suspension	Ty

\* HIS = *H influenzae suis*† *B prodigiosus* present in filtrate *H influenzae suis*, however, could not be demonstrated

*Influenza virus and H influenzae suis*

	AUTOPSY FINDINGS	<i>H influenzae suis</i>		REMARKS
		Lung	Bronchial exudate or scrapings	
12a	Very few Typical and extensive Typical	Absent Pure culture  Pure culture	Absent Pure culture  Mixed culture	Illness extremely mild More severe disease than control (871)  Control of unfiltered suspension
	Very few Typical  Negative Typical	Absent Pure culture  Absent Mixed culture	Absent Mixed culture  Mixed culture Pure culture	Illness extremely mild Disease about same severity as control (876) Control of culture alone Control of unfiltered suspension
	Few Not autopsied Typical	Absent  Mixed culture	Absent  Pure culture	Scarcely recognizable illness Scarcely recognizable illness Same severity as disease in control (895)
	Typical and extensive Negative Typical	Pure culture  Absent Mixed culture	Mixed culture  Mixed culture Not cultured	Monbund when killed Control of culture alone Control of unfiltered suspension
	Few Typical Typical Negative Typical but few	Sterile Sterile Pure culture Absent Absent	Sterile Mixed culture Mixed culture Pure culture Pure culture	Scarcely recognizable illness Same type of disease as control (913) Same type of disease as control (913) Control of culture alone Control of unfiltered suspension
	Not autopsied Not autopsied Not autopsied Typical  Not autopsied Typical	   Pure culture  Pure culture	   Pure culture  Pure culture	Scarcely recognizable illness Scarcely recognizable illness Scarcely recognizable illness More severe than disease of control (951) Control of culture alone Control of unfiltered suspension

recorded were sterile

*Effect of inocula*

EXPERI- MENT NUMBER	INFECTIOUS MATERIAL FROM SWINE, NUMBER	SWINE INOCU- LATED, NUMBER	INOCULATED INTRANASALLY WITH
1	860	859	10 cc Berkefeld N filtrate
	Strain 14 (1930)	861	8 cc Berkefeld N filtrate + 2 cc culture HIS*
	In infusion broth	871	10 cc unfiltered suspension
2	872	875	4 cc Berkefeld N filtrate
	Strain 15 (1930)	874	4 cc Berkefeld N filtrate + 2.5 cc culture HIS
	In infusion broth	873	2.5 cc culture HIS in 4 cc infusion broth
		876	4 cc unfiltered suspension
3	878	894	7 cc Berkefeld N filtrate + 2 cc sterile horse bl
	Strain 15 (1930)	897	Infected by contact with Swine 894
	In distilled water	892	7 cc Berkefeld N filtrate + 2 cc culture HIS
		896	Infected by contact with Swine 892
		893	2 cc culture HIS in 7 cc distilled water
		895	5 cc unfiltered suspension mixed with 10 cc norm swine serum
4	907	911	4 cc Berkefeld N filtrate
	Strain 15 (1930)	910	4 cc Berkefeld N filtrate + 2 cc culture HIS
	In infusion broth	915	Infected by contact with Swine 910
		912	2 cc culture HIS in 4 cc infusion broth
		913	4 cc unfiltered suspension
5	918	919	8 cc Berkefeld N filtrate †
	Strain 15 (1930)	920	8 cc Berkefeld N filtrate
	In infusion broth	921	8 cc Berkefeld N filtrate
		923	8 cc Berkefeld N filtrate + 2 cc culture HIS
		922	2 cc culture HIS in 8 cc infusion broth
		951	8 cc unfiltered suspension

\* HIS = *H influenzae suis*† *B prodigiosus* present in filtrate *H influenzae suis*, however, could not be demon

*Influenza virus and H. influenzae suis*

	AUTOPSY FINDINGS	<i>H. influenzae suis</i> IN		REMARKS
		Lung	Bronchial exudate or scrapings	
1	Very few Typical and extensive Typical	Absent Pure culture  Pure culture	Absent Pure culture  Mixed culture	Illness extremely mild More severe disease than control (871)  Control of unfiltered suspension
	Very few Typical  Negative Typical	Absent Pure culture  Absent Mixed culture	Absent Mixed culture  Mixed culture Pure culture	Illness extremely mild Disease about same severity as control (876) Control of culture alone Control of unfiltered suspension
	Few Not autopsied Typical	Absent  Mixed culture	Absent  Pure culture	Scarcely recognizable illness Scarcely recognizable illness Same severity as disease in control (895)
	Typical and extensive Negative Typical	Pure culture  Absent Mixed culture	Mixed culture  Mixed culture Not cultured	Moribund when killed  Control of culture alone Control of unfiltered suspension
	Few Typical Typical Negative Typical but few	Sterile Sterile Pure culture Absent Absent	Sterile Mixed culture Mixed culture Pure culture Pure culture	Scarcely recognizable illness Same type of disease as control (913) Same type of disease as control (913) Control of culture alone Control of unfiltered suspension
	Not autopsied Not autopsied Not autopsied Typical  Not autopsied Typical	   Pure culture  Pure culture	   Pure culture  Pure culture	Scarcely recognizable illness Scarcely recognizable illness Scarcely recognizable illness More severe than disease of control (951) Control of culture alone Control of unfiltered suspension

orded were sterile

gators of human influenza had been trying to decide between Pfeiffer's bacillus and a filtrable virus (hypothetical at the time) as the cause of that disease

*A complex etiology in swine influenza* There was one possibility which, if true, would explain the observations, perhaps swine influenza was a disease of complex etiology and both the organism and the virus were essential to its causation. This was tested experimentally by inoculating a pig intranasally with a mixture of *H influenzae suis* and the virus. It came down with swine influenza. Further experiments were carried out and in these the effect of the virus alone and the organism alone were carefully controlled. The results of 5 such experiments are outlined in table 1.

As shown in table 1, all eight of the swine infected by inoculation with Berkefeld filtered infectious material or by contact with filtrate-infected swine developed only the mild filtrate disease. In some instances it was so slight as almost to escape recognition. None of the animals exhibited a febrile reaction. Those coming to autopsy showed the scant scattered areas of pulmonary atelectasis characteristic of the filtrate disease.

The swine which were inoculated intranasally with pure cultures of *H influenzae suis* were completely negative both clinically and at autopsy.

All the swine which received mixtures of the virus and *H influenzae suis* developed a disease that was typical of swine influenza both clinically and at autopsy. Of the seven hogs infected either by direct inoculation with the virus-bacterium mixture or by contact with swine so infected, three developed a disease that was of about the same severity as that shown by the control animals inoculated with unfiltered infectious material. Two others had a mild influenza but the disease which developed in their control was also atypically mild. The remaining two swine came down with an influenza of very severe type which exceeded that developed by their controls. These experiments are interpreted to indicate that swine influenza is caused by the concerted action of a filtrable virus and *H influenzae suis*. The dilemma of too many etiological agents was thus finally solved by accepting both as essential.

The mechanism by which the two agents act in concert to cause

influenza is unknown, although several possibilities are apparent. It may be that the pathogenic activities of the virus are such as to create a portal of entry for *H. influenzae suis*, and to furnish a favorable medium in which it can multiply. There can be little doubt that, in the presence of swine influenza virus, the organism possesses invasive powers which it completely lacks when administered alone. A second possibility is that the virus is the important component in contributing to the pathology and perhaps also to the symptoms characterizing the clinical picture and that the organism, acting in the fashion of Reynals' factor (9), enhances to a marked degree the pathogenic properties of the virus, and hence the severity of the resulting disease. A third possibility, and one rendered very likely from consideration of the qualitative and quantitative differences between the pathology of the filtrate disease and swine influenza, is that the activities of both the virus and the organism are influenced by the concomitant presence of the other agent in the respiratory tract and that both actually contribute to the lesions of swine influenza.

The question of whether any bacterium other than *H. influenzae suis* can play a primary etiological rôle in swine influenza has not been exhaustively studied. However, in numerous infections of swine with virus alone none of the organisms comprising the normal respiratory tract flora has been capable of acting with the virus to cause the disease. Furthermore, the constant presence of *H. influenzae suis* in experimental infections induced by 10 strains of swine influenza collected in the autumns of five different years seems sufficient to indicate that, if not the only bacterium able to complete the etiological complex, it is at least the predominating one for the regions from which our infectious material has been obtained.

#### A FILTRABLE VIRUS IN HUMAN INFLUENZA

In 1933 Smith, Andrewes, and Laidlaw (10) transmitted a disease to ferrets by inoculating intranasally filtrates of pharyngeal washings from cases of epidemic influenza in man. The ferret disease proved to be serially transmissible, and was characterized by a 2-day incubation period, a diphasic temperature response, symptoms of nasal catarrh and variable systemic disturbances. The mucous membranes of the nasal passages of ferrets killed during the first or second febrile

periods were acutely inflamed. Histological examination revealed vascular congestion, dilated lymph channels, numerous leucocytes, and complete disappearance of ciliated cells. The causative agent possessed the properties of a filtrable virus. In their original work, Smith, Andrewes, and Laidlaw recovered the virus from the throat washings of 5 of 8 cases tested and failed to recover it from 4 subjects not suffering from influenza. Sera obtained from either recovered ferrets or from patients after an attack of influenza neutralized the virus. All the evidence first presented and that obtained later points to the etiological importance of this virus in the disease. A laboratory animal for use in studying human influenza was thus, after so many years, at hand.

Smith, Andrewes, and Laidlaw also found that swine influenza virus was infectious for ferrets and in them produced an illness similar to that caused by the virus of human origin.

The susceptibility of ferrets to swine influenza virus was easily confirmed. However, because difficulty was encountered in administering infectious suspensions intranasally some of my animals were lightly etherized prior to inoculation (11). Ferrets infected in this way developed a more severe illness than that described by the English investigators, exhibiting an extensive bloody, edematous, lobar pneumonia when autopsied on the 4th or 5th day after infection. The pneumonia sometimes terminated fatally. In contrast to influenza in swine, the ferret disease was not modified in character when cultures of *H. influenzae suis* were inoculated together with the virus.

In 1934, Francis recovered a virus from cases of epidemic influenza in Puerto Rico (12). In its earlier passages, this virus produced a disease in ferrets similar in all respects to that described for the English virus. Francis thus confirmed the observations of Smith, Andrewes, and Laidlaw that a filtrable, infectious agent could be transferred from human cases of epidemic influenza to ferrets. Furthermore, Francis found that after several passages in ferrets anesthetized at the time of inoculation, his virus produced pneumonias similar to those seen in ferrets inoculated in this way with swine virus. He pointed out that this suggested adaptation of the human virus to the ferret. Similar passage of the English strain has since resulted in its also

acquiring the ability to produce pulmonary consolidation (13) It is thus apparent, as Francis indicated, that ferret-adapted human influenza virus possesses pathogenic properties for ferrets like those shown from the beginning by swine influenza virus

#### THE INFECTION OF MICE WITH INFLUENZA VIRUS

Andrewes, Laidlaw, and Smith (14), and Francis (12) discovered independently that the human influenza virus could be transmitted to white mice after preliminary passage in ferrets

Mice inoculated intranasally, while etherized, with a mouse-adapted virus, usually showed symptoms within 24 to 48 hours Their coats appeared staring, they became less active, lost their appetites and remained huddled together in a corner of their cage Later the illness was characterized by exaggerated respiratory movements, definitely slower than those of normal mice Some of the animals died as early as the 3rd or 4th day of their illness The mortality from a heavy dose of virus approached 100 per cent At postmortem the only constant changes were in the lungs These were deep red and almost airless except for small emphysematous areas at the periphery In mice that died all lobes were usually consolidated, while in those killed early in their disease various degrees of lung involvement were seen

The virus of swine influenza also proved pathogenic for mice and produced a disease in this species which was indistinguishable clinically or pathologically from that caused by the human agent (14) There was, however, one important difference As mentioned above, the human virus required a preliminary period of adaptation in the ferret before it could be transferred to mice (15) The swine virus, on the other hand, could be transmitted directly from swine to mice without intervening ferret passage (16) Like the disease in ferrets, that in mice was not modified when *H influenzae suis* was administered together with the virus

The discovery of the susceptibility of the mouse to the viruses of human and swine influenza has made possible experimental work that was not feasible when it was necessary to use the more expensive ferrets or swine Mice have proven especially useful in studying the immunology of the influenza viruses



IMMUNOLOGICAL RELATIONSHIP BETWEEN THE VIRUSES OF HUMAN  
AND SWINE INFLUENZA

To date, strains of the human influenza virus obtained from four such widely separated localities as London (10), Puerto Rico (12), Philadelphia (17), and Melbourne (18) have been studied immunologically and found to be identical so far as could be determined (15, 17 and 18). Likewise, strains of swine influenza virus obtained in three different epizootic periods have proved immunologically the same (19). Since the character of the disease produced by the human and swine viruses in ferrets and mice was similar, the question of the antigenic relationship between the two agents arose. Smith, Andrewes, and Laidlaw (13) found that ferrets recovered from infection with either human or swine virus were usually immune to the other. However, though each virus was neutralized by admixture with homologous ferret immune serum, neutralization was inconstant if the heterologous serum was used. Thus, of 4 human virus-immune ferret sera tested against swine virus in ferrets, 2 failed to neutralize, 1 neutralized and the 4th neutralized in one test but failed in another. Of 3 swine virus-immune ferret sera, 1 neutralized human virus while the others failed.

Francis and I obtained similar results. We found that mice recovered from infection with either virus were immune to the other (16). However, the sera of animals recovered from infection with the one virus, though capable of neutralizing it, exerted little, if any, demonstrable protection against the other. Hyperimmunization of animals, especially to the human virus, tended to increase the heterologous neutralizing activity of their sera (20). The conclusion reached was that the viruses were related but not identical.

## ANTIBODIES TO HUMAN AND SWINE INFLUENZA VIRUS IN HUMAN SERA

Smith, Andrewes, and Laidlaw (13) showed that the sera of persons convalescent from influenza neutralized the human virus. Francis and Magill (21) demonstrated that these antibodies actually develop during an attack of the disease. Sera of 3 persons, bled during the acute stage of influenza, failed to neutralize human influenza virus, whereas, that obtained during their convalescence and again 6 months later did neutralize it. The presence of antibodies against the human

virus in the serum of an individual appears, therefore, to be an expression of a previous infection with that virus

Andrewes informed me in a personal communication that he and his co-workers had found antibodies neutralizing swine virus in high titer in the serum of a human adult and that they proposed further studies to determine how frequently such antibodies might be encountered. About this time Francis and Magill were undertaking a study of the neutralizing antibodies for human virus in sera from individuals of various ages and it seemed opportune in view of Andrewes' information, to study this same group of sera for their ability to neutralize swine virus. We know from experience with the sera of animals

TABLE 2  
*Human and swine influenza virus neutralizing antibodies in human sera*

AGE GROUP	EXPERIMENTS OF ANDREWES LAIDLAW AND SMITH						EXPERIMENTS OF FRANCIS MACILL AND HOPE					
	Neutralization of human virus			Neutralization of swine virus			Neutralization of human virus			Neutralization of swine virus		
	Number of sera tested	Significant neutraliza- tion		Number of sera tested	Significant neutraliza- tion		Number of sera tested	Complete neutraliza- tion		Number of sera tested	Complete neutraliza- tion	
		Number	Per cent		Number	Per cent		Number	Per cent		Number	Per cent
Under 10 years	15	5	33	14	0	0	33	16	49	27	3	11
10-19 years	21	12	57	15	10	66	12	7	58	8	5	63
Over 20 years	29	18	62	19	19	100	80	38	48	77	71	92

recovered from infection with either virus that the antibodies developed were quite specific for each type of agent (20). It seemed likely, therefore, that if antibodies neutralizing swine virus were present in human sera they could be detected independently of those effective against the human virus.

The results of the experiments conducted in England and in this country were in close agreement, as shown in table 2.

Andrewes, Laidlaw and Smith (15), arranging their cases in age groups, found that the sera from 62 per cent of the individuals over 20 years significantly neutralized the human virus, 100 per cent neutralized the swine virus. In the age group 15 to 19 years, 77 per cent neutralized human virus, while here again 100 per cent neutralized

swine virus In the age group 10 to 14 years, 42 per cent neutralized human virus, and those neutralizing swine virus had fallen to 44 per cent In the group of children under 10 years, 33 per cent neutralized human virus but not a single serum from this group neutralized swine virus They remarked on the striking fact that, while neutralizing antibodies for swine influenza virus were present in the sera of all individuals 15 years of age or older, they were completely absent in the sera from children under 10 years of age

When Francis and Magill's results (22) and my own (23) were considered in age groups similar to those used by the English workers, it was found that the sera from 48 per cent of the individuals over 20 years of age completely neutralized the human virus, 92 per cent neutralized the swine virus In the age group 10 to 19 years, 58 per cent neutralized human virus, while 63 per cent neutralized swine virus In the group of children under age 10, but not including new-born infants, 49 per cent neutralized human virus while only 11 per cent neutralized swine virus The age at which neutralizing antibodies for swine influenza virus were first regularly encountered in our experiments was 12 years, as compared with 10 years in the English experiments The contrast in the ability of adults' sera and that from children to neutralize the swine virus was, however, almost as striking as that shown by the results of Andrewes, Laidlaw, and Smith In our experiments serum from only 4 of 31 of those under 12 years of age completely neutralized the swine virus, whereas that from only 6 of 81 of those 12 years of age or older failed to do so

As already mentioned, the presence of antibodies for the human influenza virus is probably an expression of a previous infection with that virus An interpretation of the significance of antibodies for swine influenza virus in human sera, however, is more difficult because no strain of influenza virus immunologically identical with the one obtained from swine has been recovered from man The question will be considered more fully later

#### THE SUSCEPTIBILITY OF SWINE TO THE VIRUS OF HUMAN INFLUENZA

Because the pathogenic activities of human and swine influenza virus were similar in ferrets, Elkeles was led to attempt the transmission of the human agent to swine (24) He succeeded in producing

a mild illness in very young pigs inoculated intranasally under light ether narcosis. At autopsy these animals sometimes showed scattered dark red broncho-pneumonic areas of consolidation in the upper lobes of the lung. When cultures of either the human or swine influenza bacillus were added to the virus at the time of its administration, the swine developed a more severe illness. The clinical picture was characterized by a low grade fever, apathy, and loss of appetite. At autopsy varying degrees of broncho-pneumonia were encountered. Virus pathogenic for ferrets could be recovered from the pneumonic lungs. It thus appeared that Likles had produced a disease somewhat resembling swine influenza in pigs by the administration of human virus mixed with influenza bacilli of either human or swine origin.

Francis and I were able to confirm Likles' observation that swine are susceptible to human influenza virus (19). Unlike Likles, however, we did not find it necessary to use very young pigs, nor to anesthetize our animals in order to induce infections, although more extensive pulmonary lesions resulted in swine inoculated while under ether.

The human virus administered intranasally causes a disease in swine that is indistinguishable clinically and pathologically from the mild illness induced by the swine virus alone. When small amounts of the organism *H. influenzae suis* are administered with the human virus a more prostrating febrile illness usually results. This is similar to swine influenza although never so severe. At autopsy the pneumonia encountered is of the same character as that seen in swine influenza but much less extensive, seldom are more than two lobes affected (figs 8 and 9). Involved areas of lung show the same histological features encountered in swine influenza. The lumen of the bronchi are filled with leucocytes (fig 10), and the bronchial epithelium is fragmented, vacuolated, and denuded of cilia (fig 11). There is an extensive peribronchial round cell infiltration (fig 10). The alveolar walls are folded, thickened, and infiltrated with mononuclear cells (fig 12), and the alveoli themselves contain small numbers of red blood cells and leucocytes. The disease caused in swine by the human virus and *H. influenzae suis* can best be characterized as a mild swine influenza similar qualitatively but differing quantitatively from the typical disease occurring naturally in this species.



FIG 8 DORSAL ASPECT OF LUNG OF SWINE INFECTED WITH MIXTURE OF P R 8 STRAIN HUMAN INFLUENZA VIRUS AND H INFLUENZAE SUIS

There is an atelectatic pneumonia of the right cardiac lobe Animal chloroformed on 3rd day of illness

Of further interest was the observation that not all pigs inoculated with the human virus and the swine bacterium developed a more severe illness than that caused by the virus alone Some exhibited symptoms

and pulmonary lesions like those seen in the filtrate disease and in these it could be shown that *H. influenzae suis* had failed to become



FIG. 9. VENTRAL ASPECT OF SAME LUNG

The pneumonia involves all of the right cardiac lobe and lobular areas of the azygos and upper portion of the right diaphragmatic lobes

established with the virus. Instances of this nature have never been encountered in swine inoculated with swine influenza virus and

*H. influenzae suis* The facts would lead one to conclude that, in swine, the human virus possesses less invasive power than does the swine virus. Furthermore, the human virus seems to be inherently less capable of acting synergistically with a second organism than is swine influenza virus.

Since one of the characteristic features of swine influenza is its extreme contagiousness, we endeavored to determine whether the

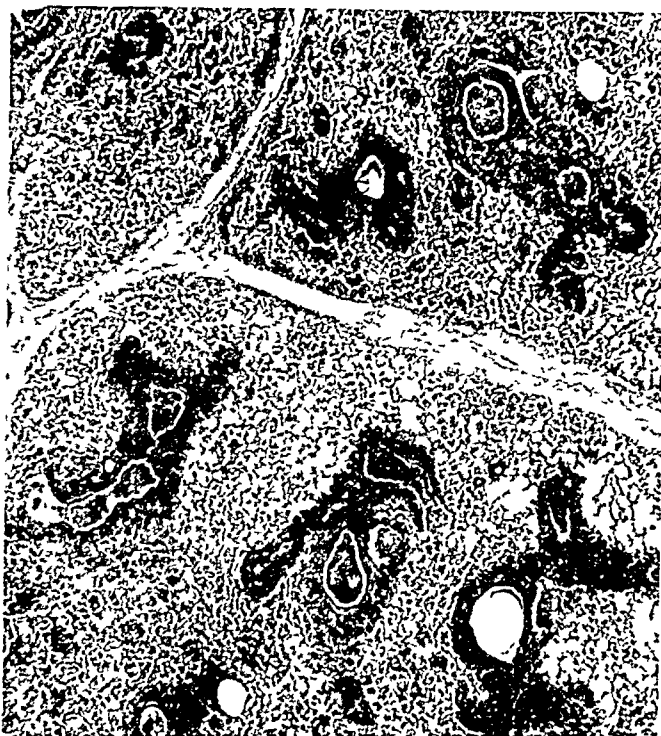


FIG. 10. SECTION OF LUNG OF A SWINE INFECTED WITH MIXTURE OF PR 8 STRAIN HUMAN INFLUENZA VIRUS AND *H. INFLUENZAE SUI*S.

The small bronchi contain a leucocytic exudate, there is a dense peribronchial round cell infiltration, the walls of the surrounding alveoli are infiltrated with round cells, and leucocytes may be seen in some of the alveoli. Animal stunned and bled to death on 3rd day following inoculation. Phloxine-methylene blue.  $\times 34$ .

human virus was also highly communicable in swine. We found that it was not, and that it thus differed significantly in this respect from swine influenza virus. However, the human virus could be transmitted serially in swine by intranasal inoculation of swine of each succeeding passage with virus derived from the lung of the infected animal of the preceding passage. The pathogenic properties of virus trans-



FIG. 11. SECTION OF A SMALL BRONCHUS IN LUNG OF A SWINE INFECTED WITH MIXTURE OF P R 8 STRAIN HUMAN INFLUENZA VIRUS AND H INFLUENZA SUI SHOWING LEUCOCYTIC BRONCHIAL INFLAMMATION, FRAGMENTED AND VACUOLATED EPITHELIUM DEFENDING OF CILIA AND ROUND CELL INFILTRATION OF THE SUBMUCOSA.

Leucocytes have invaded the mucosa. Animal chloroformed on 3rd day following inoculation. Phloxine methylene blue.  $\times 308$ .



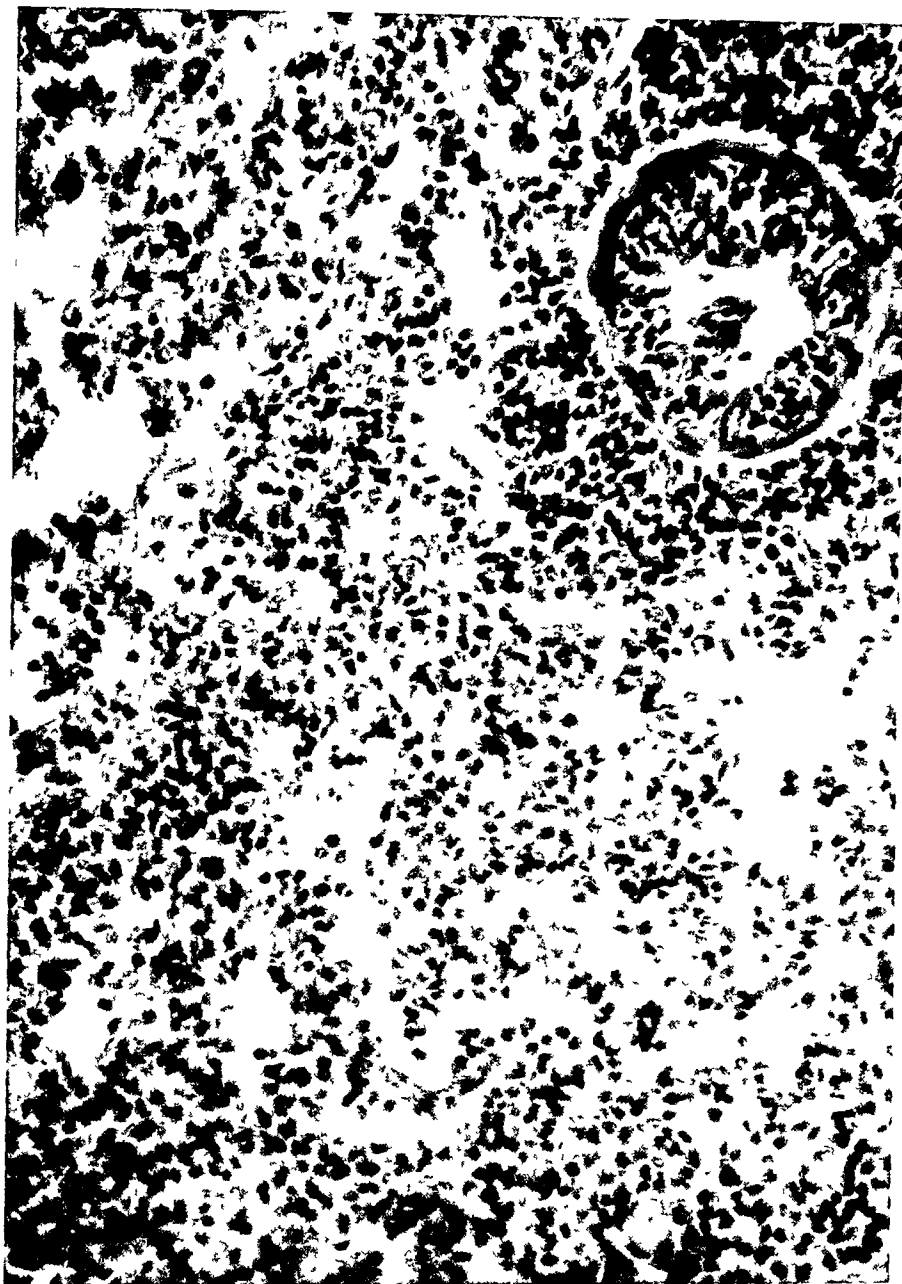


FIG 12 SECTION OF LUNG OF A SWINE INFECTED WITH P R 8 STRAIN HUMAN INFLUENZA VIRUS SHOWING ROUND CELL INFILTRATION OF THE ALVEOLAR WALLS IN AN AREA OF ATLECTASIS

Animal chloroformed on 3rd day following inoculation Phloxine-methylene blue  
× 308

mitted in this way for 5 serial passages were not altered for either swine or mice, that is, there was no evidence of further adaptation of the virus to swine. Also its immunological identity remained intact.

#### DISCUSSION

The facts brought out by recent studies of swine and human influenza have been presented. I should like now to discuss these in an effort to point out the possible relationship between the two diseases and to indicate what knowledge, gained by study of swine influenza, may be applicable to the human disease.

As was stated earlier, many middle western veterinarians and farmers were, in 1918, impressed by the similarity between hog flu and the influenza then prevalent in man and suspected that the two conditions might be causally related. Two facts, brought to light early in our experimental work, suggested that these popular suspicions might be correct. The first had to do with the presence of a leucopenia in swine influenza. The second concerned the similarity of the predominant bacterium encountered in swine influenza to that long believed to be the cause or one of the causes of human influenza. The observation that a filtrable virus was etiologically essential in swine influenza, on the other hand, was predicted by no advance information concerning the human disease and it was not until Smith, Andrewes, and Laidlaw recovered a virus from cases of influenza in man that a human agent was available for comparison.

The results of this comparison have been given earlier but require further discussion. The viruses from both swine and man were found to be pathogenic for ferrets, although the human agent possessed less initial pathogenicity for this species than that from swine. Etherization of ferrets at the time of inoculation enhanced the pneumonia-producing activity of each virus. Both viruses proved fatally pathogenic for white mice except that here a preliminary period of adaptation in the ferret was required for the human but not for the swine virus. It seems likely that these initial differences in the pathogenic activities of the two agents may be those due to "fixation" by prolonged sojourn in a foreign host, since passage of human influenza virus through ferrets alters it in such a way that it becomes more like the swine influenza virus and less like the one originally obtained from



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Animal chloroformed on 3rd day following inoculation Phloxine-methylene blue  
× 308

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man Human influenza virus, fully adapted to the ferret, produces a clinical and pathological picture in ferrets and mice that is indistinguishable from that caused in these animals by swine virus

But the similarity does not end here, the two agents are immunologically related Ferrets, mice, or swine recovered from infection with one virus are usually solidly immune to the other However, the sera of such immune animals, although neutralizing the homologous virus perfectly, exert as a rule little or no neutralizing action against the heterologous virus

The above facts demonstrate that the viruses from man and swine, while undoubtedly possessing some antigenic elements in common and producing similar disease manifestations in ferrets and mice, are not identical and can be distinguished from each other immunologically So far as they go, these data indicate that the swine virus is specific for swine, and that it is different from the one currently prevalent in man

However, when the sera from human beings were tested for their ability to neutralize the human and swine influenza viruses the results were such as again to focus attention on the possibility that the swine virus had at some time in the past been a human pathogen It was found, as expected, that sera from many people of all ages neutralized the human virus It was surprising though to discover that sera from most adults also neutralized the swine virus We knew from experience with sera of animals immune to either the human or swine agent that the neutralization test was quite accurate in denoting the type involved in previous infections There was no reason for supposing that, with human sera, it would be less exact in indicating the type of virus causing previous infections in man The one disturbing possibility was that in man, as in the case of some animals (20), repeated exposures to human virus might result in the establishment of antibodies effective against both viruses Comparison of duplicate tests against the two types demonstrated clearly that antibodies neutralizing swine virus were frequently present in human sera that failed to neutralize human virus In these it was evident that the neutralizing antibodies for swine influenza virus had not resulted from previous infections with human virus It seemed most probable that their presence indicated a past infection with a virus having an antigenic composition similar to that of swine influenza

It is apparent from these findings that human sera contain neutralizing antibodies for at least two immunologically distinct types of influenza virus. One is the current human virus of Smith, Andrewes, and Laidlaw known to be widely prevalent in man at the present time. The other, of an antigenic composition similar to swine influenza virus, is unknown and has never been detected in man. It has, however, left ample evidence of its past widespread prevalence in the form of neutralizing antibodies in the sera of almost all adult human beings. That it is no longer widely existent in the human population is indicated not only by the failure of investigators to recover it from cases of influenza during the past two years, but by the almost complete absence of antibodies specific for it in the sera of children under 10 years of age. Unless one wishes to ascribe a non-specific character to the swine virus-neutralizing antibodies in human sera, the conclusion that this unknown human virus was indeed swine influenza virus, or a closely related agent, is inescapable.

However, there is no direct evidence that the swine influenza virus, as we know it today, is capable of infecting man. Indeed, indirect evidence indicates that it does not infect man because, while swine influenza has occurred annually since 1918, our serological evidence suggests that the human prototype of swine influenza virus ceased infecting man generally at least ten years ago.

The most apparent interpretation of these findings is that the swine virus represents a surviving form of an extinct or temporarily quiescent human influenza virus and that it has become so "fixed" in swine as to be no longer pathogenic for human beings. If this is the case, when the history that swine influenza appeared for the first time in 1918 serves to date the time of prevalence of this vanished human virus. It is believed that the experimental and historical facts are best explained by the theory that swine influenza virus represents a surviving form of that pandemic in man in 1918, as already suggested by Laidlaw (25), and that it has not had its immunological identity detectably altered by its prolonged sojourn in hogs. On this basis, the presence in human sera of antibodies neutralizing swine virus would be considered to indicate that the donors of these sera had undergone an immunizing exposure to, or infection with, an influenza virus of the 1918 pandemic type.

There can be little doubt that recent human influenza of the type

man Human influenza virus, fully adapted to the ferret, produces a clinical and pathological picture in ferrets and mice that is indistinguishable from that caused in these animals by swine virus

But the similarity does not end here, the two agents are immunologically related Ferrets, mice, or swine recovered from infection with one virus are usually solidly immune to the other However, the sera of such immune animals, although neutralizing the homologous virus perfectly, exert as a rule little or no neutralizing action against the heterologous virus.

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from which Smith, Andrewes, and Laidlaw and Francis recovered their viruses is a benign ailment compared to that rampant in 1918. It might be expected that this difference would be apparent in the character of the disease produced by the two viruses in experimental animals, assuming the swine virus to be representative of the 1918 human type. So far as ferrets and mice are concerned, it is doubtful whether even an experienced observer could certainly differentiate by clinical or postmortem examination between the diseases caused by the two viruses once they are established in these animals. However, in the hog, differences are apparent. If it could be postulated, for the sake of the present discussion, first that swine influenza etiologically is a replica of the human pandemic disease, and second that swine and man react alike to infection with virus and bacterium, then the differences in the behavior of swine and human influenza virus in the swine might very well reflect differences between severe pandemic and milder interpandemic human influenza. Under this assumption, two dissimilarities between the swine and human viruses, so far as their behavior in swine is concerned, acquire importance. The first has to do with communicability. The disease caused by the swine influenza virus is highly contagious, while the human virus is of low communicability. The other concerns the ability of the two viruses to act synergistically with a second organism. Swine virus administered in combination with *H. influenzae suis* causes a prostrating illness, an extensive pneumonia, and the bacterium always establishes itself in the respiratory tract. The human virus, on the other hand, given in combination with the same organism, causes a less prostrating illness, a less extensive pneumonia and, not infrequently, the bacterium fails to establish itself along with the virus in the lower respiratory tract. Differences such as these in the pathogenic properties of two closely related agents could readily account for epidemiological and clinical differences in the diseases they caused.

Incidentally, in view of the low communicability in swine of the strain of human influenza virus recently prevalent, it seems unlikely that it could establish itself in this species and progress to cause any widespread or serious epizootic disease such as the 1918 pandemic virus supposedly did.

Thus far the discussion has concerned mainly the viruses involved

in the influenzas of swine and man. What of the rôles played by bacteria associated with them, *H. influenzae suis* in the swine disease, and *H. influenzae*, streptococci, pneumococci, and other organisms, in the human disease? I can speak with certainty only regarding swine influenza. Here *H. influenzae suis* must be considered a definite and indispensable part of the etiological complex. It is always present in the respiratory tracts of swine ill of the disease, under natural or experimental conditions it transfers with the virus in series from swine to swine, it can be substituted by no other known swine pathogen, a disease similar to the naturally occurring swine influenza results only when it accompanies the virus in experimental infections, and it enhances the activity of the virus in a constant and predictable fashion. I can think of no reason for relegating it to the role of secondary invader unless one wished arbitrarily to consider the mild filtrate disease caused by the virus alone as true swine influenza and the natural disease, diagnosed as such in the field, as something else. There is no evidence to indicate that the filtrate disease exists as a natural infection of swine or that the virus ever invades swine, under farmyard conditions, unaccompanied by the organism.

The similarity of *H. influenzae suis* to *H. influenzae* suggests that, like the swine influenza virus, it may have had its origin in man. Because of the apparent indispensability of the organism to the virus in causing the disease, it seems most likely that both entered swine at the same time. It would indeed be difficult to conceive that a bacterium, possessing the potential pathogenicity of this organism, should long persist as an unknown saprophyte in swine and acquire recognition only when a low grade virus happened along to supplement its latent disease-producing capacity.

If *H. influenzae suis* actually did transfer with the virus from man to swine in 1918, and if it is a direct descendant of the *H. influenzae* then prevalent, we must ask why, of all the other organisms known to be involved in human influenza of that time, it alone became established in swine. A possible answer, if one wishes to maintain an analogy between the swine and human diseases, is that pandemic human influenza, like swine influenza, may be a disease of definite complex etiology and swine passage may have served to segregate the two essential etiological components from the assortment of strepto-

cocci, pneumococci, and other organisms secondarily involved. Separation and isolation of pathogenic microorganisms from mixtures by inoculation of experimental animals is a well-known and accepted laboratory procedure, and it is reasonable to suppose that it might occur under natural conditions.

However, it may be a mistake to attempt too close a comparison between swine and pandemic human influenza by insisting that *H. influenzae suis* and *H. influenzae* play analogous rôles respectively in the two diseases. It is possible that, in the human disease, any one of a large number of pathogenic microorganisms can act with the virus to cause a severe illness and that, of these, only *H. influenzae* could become established in swine. Thus in 1918, while the human disease may have been caused by the virus in conjunction with pneumococci, streptococci, *H. influenzae* and other microorganisms, the infections that became established in swine were always those only of the virus and *H. influenzae* because these two agents, of all those involved in the human disease, may have been the only ones suited to an existence in the swine respiratory tract.

A last possibility which must be kept in mind is that human beings may react to infection with influenza virus in the same fashion as ferrets and mice. In this event the virus would be considered the sole and primary etiological agent and the bacteria encountered would be thought of as merely concomitant and of secondary importance. Certainly, were it not for swine influenza with its known complex etiology of virus and bacterium, it seems likely that the recently discovered human influenza virus might now prove entirely acceptable as the sole cause of human influenza on the basis of its pathogenic activities in ferrets and mice. However, the disease caused in ferrets and mice by the human influenza virus may be just as highly artificial in reflecting the complete etiology of human influenza as is that caused in the same animals by swine influenza virus in reflecting the complete etiology of the swine disease. I think it would be a mistake, at this time, to focus all of our attention on this new virus and to neglect further study of the bacteriology of influenza. It seems to me that all of the facts at our disposal point toward the probability that the virus of human influenza, like that of swine influenza, constitutes only a partial etiology of the disease in which it is involved, and that, with

respect to the influenza he suffers, man probably resembles the hog more closely than he does the ferret or mouse

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## THE SIGNIFICANCE OF ALLERGY IN DISEASE

EUGENE L. OPIE

Usage concerning the meaning of allergy varies widely and it seems desirable to apply this term, as originally proposed by von Pirquet (1906), to the changed state in relation to antigens that follows their introduction into the body rather than to the phenomena of sensitization alone. In this sense it includes both the tissue changes at the site of contact with antigen and the acute functional disturbances, such as anaphylactic shock, following dissemination of antigen by way of the blood stream. In view of its origin and subsequent use it is inadvisable to apply it to changes not related to the phenomena of immunity.

### ALLERGY IMMUNITY AND SENSITIZATION

Anaphylactic shock is an artificial phenomenon induced by the experimental or therapeutic injection of foreign substances into the circulating blood and seldom occurs in the usual course of nature or during spontaneous disease. Injurious agents ordinarily enter tissue spaces after they have penetrated the skin or the mucous membranes that separate the body from the exterior. In the tissue spaces dissemination proceeds slowly and the inflammatory reaction of the sensitized animal brings to the injured spot exuded fluid and wandering cells, this exuded fluid contains the antibodies that are present in the plasma. Tissue sensitization is manifested by the ability to react with intensified inflammation and perhaps necrosis to an irritant that ordinarily produces scant inflammation. Foreign protein or tuberculin introduced into the tissues of a normal animal produces a clearly definable but mild inflammatory reaction but in a sensitized animal causes superficially evident hyperemia and edema. The term "allergic inflammation" is applicable to the local reaction of sensitization. Terms such as hyperergy, anergy and hypoergy, normergy and pathergy, parergy and heterergy, are often used in the unconscious effort to substitute definable word symbols for vaguely definable phenomena.

Both anaphylactic shock and allergic inflammation produced by

foreign proteins are antigen-antibody reactions, subject to passive transfer and to desensitization by excess of antigen. It is noteworthy that anaphylactic shock can be passively produced by reversing the order of introducing antigen and antibody, that is, by passively preparing with antigen introduced into the blood stream and later introducing antibody by the same route (Opie and Furth, 1926). This reversed reaction has served to remove some of the mystery from anaphylaxis (Doerr, 1929) because it shows that anaphylaxis occurs when antigen and antibody meet, and the same statement is demonstrably applicable to allergic inflammation produced by foreign protein (Opie, 1924).

Foreign erythrocytes injected into the skin of guinea pigs sensitized to them remained intact for at least a week (Rossle, 1914). Levandowsky (1916) found that tubercle bacilli applied to the scarified skin of a tuberculous animal produced an acute inflammatory reaction (Koch phenomenon) with necrosis, remained intact within the necrotic material and were in large part cast off with it between the fourth and seventh days after inoculation.

The fate of foreign protein at the site of allergic inflammation (Arthus phenomenon) is better known than that of other similar agents. For example, crystalline egg albumen, introduced into the skin of a normal rabbit spreads widely but produces scant inflammation and readily enters the circulating blood. In the allergic animal it produces intense inflammation (Arthus phenomenon), remains localized and fails to enter the blood (Opie, 1924). Both inflammation and antibodies favor the local fixation of the antigen, their relative importance is measured with difficulty.

The tuberculin-like reactions have characters of their own, for they are elicited in sensitized animals by substances, e.g. tuberculin, that apparently do not have the characters of an antigen and cannot produce sensitization or immunity. Rich and Lewis (1932) have made the significant observation that cells of tuberculous animals are destroyed *in vitro* by the addition of tuberculin, whereas those of normal animals are unaffected. Aronson (1933) was unable to demonstrate a similar relation between the cells of animals sensitized to foreign protein and the sensitizing substance. Some hypothetical agent or antibody responsible for sensitization to tuberculin may be

fixed to tissue cells more intimately than that which is associated with protein sensitization (see Freund, 1929)

No attempt will be made to define the nature of asthma, hay fever and similar conditions. The relation of "atopens" (Coca and Cooke, 1923) to antigens is as yet ill-defined and the domain of "atopic" sensitization requires further exploration. Passive atopic sensitization is the basis of a reaction that can be used quantitatively. The suggestion that this form of sensitization may be inborn or constitutional and unrelated to previous contact with the agent that reveals it, would if sustained, separate it from other forms of sensitization.

Allergy, in accordance with the meaning assigned to it by von Pirquet (1906), is, as with tuberculous infection, characterized by sensitization and immunity. Sensitization is manifested by heightened reaction to injury, that is, by allergic inflammation, which in its severest form, as with other inflammation, is associated with necrosis of tissue. Manifestations of immunity are antibody formation and increased resistance to infection. It is very well known that in some infections immunity may occur with inconspicuous, if any, sensitization. Allergic inflammation is one of the characteristic phenomena of tuberculosis of man and of the guinea pig, but is not evident with tuberculous infection of rat or of dog. Angevine (1936) produced intense sensitization with an avirulent strain of hemolytic streptococcus and little with a virulent strain. Toxins may produce sensitization but antitoxic immunity is usually unaccompanied by evident sensitization.

Even should we assume that sensitization and resistance are dependent upon identical antibodies no constant parallel between the two should be expected, for the manifestation of allergic inflammation on the one hand and resistance to bacterial invasion on the other are each dependent on factors peculiar to itself. Furthermore, antigens of bacteria and of serum, for example, are usually multiple and not simple antigens. A rabbit treated with crystalline egg albumen may be completely desensitized by injecting this substance into the blood stream, antibodies disappear from the blood and allergic inflammation is no longer obtainable (Opie, 1924). With complex antigens such as horse serum or egg white, on the contrary, complete loss of skin sensitization and of antibodies fails to occur. Desensitization to allergic inflamma-



tion (Rich, Jennings and Downing, 1933) is compatible with immunity if the two are referable to different antigen fractions. Indeed, continued efforts to maintain desensitization during the course of a chronic disease such as tuberculosis might by repeated injection of antigens increase rather than diminish immunization as (in experiments of Derrick, Branch and Crane, 1935)

(1) Allergic inflammation fixes antigen at the site of its penetration into the tissues, prevents its entrance into the blood stream and thus prevents anaphylactic shock and other injury of internal organs

(2) Tissue sensitization manifested by allergic inflammation on the one hand and immunity on the other may occur separately, the two do not necessarily pursue a parallel course and desensitization may eliminate one but not the other. Nevertheless it is not evident that they are wholly independent phenomena

#### ALLERGY DURING THE COURSE OF DISEASE

Tuberculosis affords the best illustration of changes in the course of a disease referable to allergy. The adult or reinfection type of pulmonary tuberculosis owes its peculiar characters to immunity and sensitization following a first infection. It would not be profitable at the present time to discuss the relation of sensitization to resistance in diseases such as syphilis, typhoid fever, or undulant fever, in which the luetin, typhoidin or abortin reaction gives more or less decisive information concerning tissue sensitization to products of the microorganisms concerned. The following discussion will be limited to the allergic phenomena of tuberculosis and of streptococcus infections because the evidence that has accumulated, in great part experimental, helps to define the limitation of present knowledge concerning the relation of sensitization to immunity.

*Tuberculosis* Attempts to interpret the symptoms and lesions of human tuberculosis, e g tuberculous pneumonia, caseation or cavity formation, in terms of sensitization would be unprofitable with present knowledge but experimental observations give significant information concerning the influence of allergic inflammation upon the pathogenesis of the disease.

Tubercles are formed more rapidly in the allergic than in the normal animal and recent observations have shown that both polymor-

phonuclear leucocytes and macrophages accumulate more rapidly in the former. In the lungs, liver, spleen and other organs of allergic animals that resist infection, tubercle bacilli are destroyed more rapidly than in animals that have been normal before inoculation (Lurie, 1929). Sensitization under certain conditions may favor the occurrence of caseation but in general tuberculous lesions are more extensive and caseation less conspicuous in allergic than in previously normal animals provided the microorganism is not present in such number that it multiplies without restraint. Resolution of tuberculous pneumonia occurs more readily in the allergic animal (Nichols, 1905, Burke, 1935). The sensitized animals react to infection with greater intensity than normal animals and the mass of newly formed tissue may be more extensive for a time in the former, but ultimately these lesions retrogress and the animals that temporarily seemed more susceptible show resistance considerably in excess of that of animals normal at the time of inoculation.

During the course of experimental tuberculous infection, sensitization manifested by the tuberculin reaction on the one hand and antibody formation best measured by complement fixation on the other do not pursue a parallel course. Following inoculation both are evident within from two to three weeks, increase to a maximum and remain elevated, the intensity of the tuberculin reaction is subject to considerable variation but the titer of complement fixation tends to remain constant. Several weeks before death skin sensitization diminishes and usually disappears but complement fixation is almost unchanged (Freund, Laidlaw and Mansfield, 1936). It is noteworthy that desensitization may be produced by administration of a considerable quantity of tuberculin, so that the skin reaction disappears completely but the titer of complement fixation is only slightly reduced (Freund and Mansfield, 1936).

In reinfected guinea pigs Krause and Willis (1925) found that tubercle bacilli pass more slowly from the site of injection to the neighboring lymph nodes than in previously normal animals. Inoculation of excised tissue into guinea pigs demonstrated that the passage in the normal animal occurred in 24 hours, whereas in the reinfected animal it required two or three weeks. They attributed this retardation to fixation of bacteria at the site of a heightened inflammatory

reaction In rabbits repeatedly injected with dead tubercle bacilli Freund (1932) and Freund and Angevine (1936) found similar inhibition of dissemination when human tubercle bacilli were inoculated into the skin but very little was evident when the more virulent bovine bacillus was used

*Infection with non-hemolytic streptococci* Hypersensitiveness following inoculation with non-hemolytic streptococci (pathogenic strains of *Streptococcus viridans* and numerous strains of indifferent streptococci) has been carefully studied in rabbits by Swift and his co-workers This condition is characterized by increased reactivity of the skin after intracutaneous inoculation, corneal inflammation produced by bacterial sediment and toxic reactions following intravenous injection (Derrick and Swift, 1929) These reactions are regarded as analogous to those produced by tuberculin because they were not demonstrably dependent upon the presence of antibodies in the serum and could not be transferred passively from one animal to another (Derrick and Andrews, 1926)

The site of injection influences profoundly sensitization to non-hemolytic streptococci Rabbits can be made sensitive by repeated intracutaneous injections of streptococci so that subsequent skin inoculation produces greatly exaggerated lesions (Derrick and Andrews and Swift, 1926), intravenous injections on the contrary increase resistance against invasion of the skin so that the resulting lesion is smaller than that produced by cutaneous inoculation of normal animals (Swift and Derrick, 1929) These phenomena have been analyzed by McEwen and Swift (1935), intravenous inoculation produces scant skin sensitization to the intact cocci, to their nucleoprotein or to their carbohydrate fraction, but induces the formation of abundant agglutinating or precipitating antibodies to them Intracutaneous inoculation produces skin sensitization to the cocci themselves, to nucleoproteins and to the carbohydrate fraction, but no demonstrable antibodies to these substances It is evident that agglutininogen and precipitinogen do not enter the blood stream from the site of cutaneous inoculation in sufficient quantity to bring about the formation of the corresponding antibodies

A phenomenon of much significance from the standpoint of the pathogenesis of disease recalling the focal reaction of tuberculin has

been described by Andrews, Derrick and Swift (1926) When non-hemolytic streptococci including green-producing and indifferent strains are injected into the skin of rabbits they produce a focus of inflammation that reaches a maximum size in from 24 to 48 hours and then retrogresses, about the eighth or ninth day in many animals the lesion increases conspicuously in size, remains enlarged during two or three days, and then disappears Coincident with the appearance of this secondary reaction the animal has become hypersensitive to the streptococci with which it has been inoculated and exhibits cutaneous, corneal and toxic reactions similar to those produced by tuberculin (Derrick and Swift, 1929) It is assumed that a sufficient amount of residual antigen remains at the site of inoculation to react by recurrence of acute inflammation when the animal has developed hypersensitiveness as the result of inoculation with the microorganism

Many observers have reached the conclusion that tubercle formation is essential to the production of sensitization to products of the tubercle bacillus Multiple small quantities of non-hemolytic streptococci introduced into the skin produced more effective sensitization than a single large inoculum (Derrick, Hitchcock and Swift, 1930) The tuberculin type of sensitization associated with infection by tubercle bacilli, streptococci and doubtless many other microorganisms is caused by some agent, not demonstrable by the usual tests for antibodies, it arises perhaps in local lesions and finds its way by the blood stream to other tissues of the body It forms a very intimate union with them and brings about sensitization

*Infection with hemolytic streptococci* Sensitization during the course of infection with hemolytic streptococci has characters that deserve consideration Avirulent hemolytic streptococci repeatedly injected into the skin of rabbits cause sensitization characterized by more intense inflammation and more necrosis than in the normal animal (Angevine, 1934), the lesion is more sharply circumscribed The microorganism multiplies more rapidly during the first five hours at the site of injection than in normal animals and persists somewhat longer When injected into the skin of the flank of sensitized rabbits streptococci reach the inguinal lymph nodes in much smaller number than in the normal animal and only during the first hour after inoculation In the normal animal streptococci pass from the superficial to the deep

lymph nodes and reach the blood or internal organs, but in the sensitized animals none are found in deep lymph nodes, blood or internal organs. In sensitized animals injury with necrosis at the site of injection favors the local multiplication of streptococci and explains their survival at a time when they have disappeared in the controls. In association with the more intense inflammatory reaction in sensitized animals streptococci are fixed at the site of entry, pass to lymph nodes in much smaller number and fail to reach the blood or internal organs.

Virulent streptococci, unlike the avirulent, are characterized by their ability to spread widely in the tissue of normal animals and to enter lymph nodes, blood stream and internal organs (Angevine, 1936). Repeated inoculation causes immunization with inhibition of these invasive characters. The virulent microorganism is a very effective immunizing agent and the animal that has received virulent hemolytic streptococci reacts with diminishing severity to the living microorganism and its products. The virulence of a microorganism which is one factor that determines its ability to injure tissue and spread in the body is perhaps dependent on some agent that may produce an immunity opposed to the phenomena of sensitization. Virulence and sensitization are perhaps dependent upon different antigens.

Experiments of Dochez and Sherman (1925) have shown that it is possible to sensitize guinea pigs to filtrates of scarlatinal streptococci and since these skin reactions are neutralized by antitoxic sera it has been suggested that sensitization has been caused by toxin. With filtrate from streptococcus of erysipelas Dochez and Stevens (1927) have found that skin reactions in the early stages of sensitization are produced by a thermolabile constituent of the filtrate and are prevented by mixing the filtrate with antitoxin. At a later stage reactions are produced by heated filtrate and can no longer be neutralized. These experiments have been cited by those who support the suggestion that the rash of scarlet fever is a sensitization phenomenon. Mackie and McLachlin (1927) and Hooker (1933) have made observations contrary to them and the latter has assembled evidence which, as he believes, demonstrates the toxic origin of the scarlatinal rash.

*Allergic inflammation and eosinophilia* A brief discussion of the relation of eosinophilia to tissue sensitization may be appended to the

present consideration of the influence of allergy on the course of disease. A heightened inflammatory reaction with accelerated accumulation of both granulocytes and mononuclear cells is characteristic of tissue sensitization. It is noteworthy that it follows the usual course of inflammation with primary exudation of polymorphonuclear granulocytes followed by accumulation of histiocytes with ability to act as phagocytes. The local eosinophilia and the eosinophile leucocytosis of asthma are well known and the relation of eosinophilia to sensitization has been much discussed. Schlecht and Schwenken (1912), Herrick (1913), and others have maintained that a first injection of extract prepared from an entozoan parasite produces no eosinophilia but with repeated injections it becomes evident. The illuminating study of Weinberg and Seguin (1914) has shown that products of certain parasitic worms, namely, fluid from echinococcus cysts or extract of hookworms, bring about local accumulation of eosinophiles when they are first introduced into the tissues. Repeated injections greatly accelerate the local accumulation of eosinophiles and increase the number of eosinophiles in the blood to from 11 to 35 per cent. In guinea pigs sensitized to horse serum and to egg white, Longcope (1913) found local eosinophilia but none in rabbits or in cats. Sensitization intensifies the accumulation of eosinophiles as well as that of other wandering cells.

#### ALLERGIC DISEASE

The foregoing discussion has shown that the course and lesions of certain infectious diseases are profoundly modified by the phenomena of sensitization. An essentially different relation is proposed by the hypothesis that certain diseases, for example, rheumatic fever and asthma, are allergic diseases. This hypothesis assumes that sensitization to the action of a microorganism, a group of microorganisms or some other substance precedes the impact with the inciting agent that produces the disease, that is, the individual must be sensitized before he can acquire the disease.

*Allergic inflammation produced by foreign protein.* Foreign protein introduced into sensitized animals produces conspicuous changes which a considerable group of observers maintain are characteristic of "allergic" disease and constitute a model for its recognition. It is

generally agreed that the essential characters of "serum disease" are referable to allergic phenomena

Much emphasis has been placed upon the swelling of connective tissue fibrils described by Gerlach (1923) in association with the Arthus phenomenon, and usually designated fibrinoid degeneration. With swelling of collagenous fibrils fibrous bundles become homogeneous. The change is associated with oedema and the swollen intercellular substance often gives the staining reactions of fibrin. Some pathologists regard this lesion as characteristic of allergic disease. Klinge (1929) has injected horse serum into the joint cavity of rabbits and has found in the adjacent soft tissue foci of necrosis characterized by this form of collagenous degeneration. On their periphery there is a cellular reaction with proliferation of histiocytes and occasional formation of giant cells.


Many experiments have been performed to determine what lesions are produced by foreign protein introduced into the blood stream of animals sensitized to it. Longcope (1913) has found that repeated intravenous injection of horse serum causes necrosis of muscle fibers of the heart associated with accumulation of mononuclear cells and ultimate formation of patches of fibrous tissue. Focal necrosis at the periphery of the liver lobule is followed by new formation of fibrous tissue. In the kidney in association with albuminuria there is necrosis of epithelium, especially of the loops of Henle and collecting tubules, and accumulation of mononuclear cells. Less conspicuous are changes in the glomeruli characterized by proliferation of endothelial cells of the capillaries, occasionally by proliferation of capsular epithelium with crescent formation, in the later stages by hyaline degeneration of glomeruli.

It is noteworthy that repeated injection of substances into the blood stream is not well adapted to determine the relation of sensitization to the production of lesions, recurrent injury may produce grave change in the absence of sensitization. To exclude this possibility sensitization may be produced by subcutaneous injection of the antigen followed by a single intravascular injection.

Foreign serum introduced into the blood stream of a sensitized animal seldom produces conspicuous inflammation in the heart, liver, kidney and other organs unless the quantity administered is very

large Vaubel (1932) has produced arteritis only when he injected serum in great quantity (10 to 30 cc) into the venous system of sensitized rabbits. Knepper (1935) has suggested that the endothelium affords an effective barrier against the penetration of foreign protein into sensitized tissue. Direct injection of serum into the ligatured blood vessel of an animal sensitized to it (Migounow, 1934) produces, as it may be expected, acute inflammation of the vessel wall, comparable to the Arthus phenomenon of the skin. Under similar conditions serum injected into renal artery with temporary compression of artery and vein is followed by inflammatory changes in the kidney with proliferation of capillary endothelium of the glomerular tufts (Masugi and Sato, 1934).

Much attention has been given to the conditions that permit foreign protein to pass from the blood stream and produce local lesions of internal organs. Auer (1920) showed that the ear of a rabbit sensitized with horse serum undergoes necrosis if preceding the injection of the serum the ear has been gently rubbed with xylol. He assumes that the inflammation caused by xylol brings about the accumulation of the antigen within the tissues of the ear and here reacts with the sensitized tissue. Heat (immersion of the ear in water at 40°C for a half hour) and cold (snow applied to the thigh for a half hour) similarly cause localized allergic inflammation at the site of irritation (Knepper, 1935). Several writers have found in these experiments a partial explanation of the characteristic localization of lesions they regard as allergic in rheumatism and other diseases, but the nature of the sensitizing antigen and of the localizing agent are both uncertain. Knepper (1934) believes that he has reproduced the hepatic and renal lesions of eclampsia by repeated simultaneous injections of horse serum and hormone of the posterior lobe of the hypophysis, injurious action of the hormones in large amount he believes causes injury to the liver and brings antigen into contact with sensitized tissue.

Morphological similarity between lesions of arteries and veins produced by intravascular injection of foreign serum in large quantity into sensitized animals and those in necrotizing arteritis or periarteritis nodosa has been noted (Klinger and Vaubel, 1931, Masugi and Isibasi, 1936), the occurrence  generation of white fibrous



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tissue being regarded as especially significant. The experimental evidence described by Knepper (1935) in support of the suggestion that peptic ulcer and cirrhosis may be produced by allergic inflammation in association with excessive use of alcohol is not convincing.

*Rheumatic fever* The occurrence of polyarthritides in association with serum sickness has suggested an analogy with rheumatic fever, a good many years ago (Weintraub, 1913). Injection of foreign serum (Friedberger, 1931) into joints of animals sensitized to the same serum, as it might be expected, usually causes severe arthritis, but efforts to sensitize the joints themselves by products of streptococci so that the microorganism later introduced into the blood stream produces arthritis have failed (Swift and Boots, 1923).

Skin sensitization to products of streptococci occurs in association with rheumatic fever. Patients with the disease react more frequently to cutaneous injection of filtrates or of nucleo-proteins from indifferent and from green streptococci than other persons with no evidence of rheumatic disease (Birkhaug, 1927, Kaiser, 1928, Swift, Wilson and Todd, 1929). Febrile responses of rheumatic patients to intravenous injection of products of streptococci (Small, 1927, Swift, Hitchcock and Derrick, 1928) are similar to the toxic reaction of tuberculous patients to tuberculin. Hypersensitiveness with rheumatic fever includes streptococci as a group and is not specific for one type. It is, however, noteworthy that many persons with no rheumatic disease are sensitive to products of streptococci (Bristol, 1923, Mackenzie and Hanger, 1927).

By injecting foreign serum into the joints of rabbits sensitized to the same serum Klinge (1929) has produced local and generalized changes which he regards as analogous to those of rheumatic fever. The so-called fibrinoid degeneration of fibrous tissue with surrounding cellular reaction occurs in the soft tissues of the joint. After serum injection into the joints of sensitized animals Klinge finds changes in the myocardium and in other tissues similar to those that follow intravenous injection and, he believes, reproduce the essential histological features of rheumatic lesions. His opinion that lesions produced by foreign serum in sensitized animals are characteristic of allergic inflammation and serve to identify the allergic origin of human disease has been accepted by a number of pathologists. The peculiar lesion of rheu-

matic fever, namely, the Aschoff body, with its fibrinoid degeneration and cellular proliferation is, they believe, a typical instance of allergic inflammation. Nevertheless, Aschoff (1935) states that the lesions of serum sensitization do not accurately reproduce those of rheumatic fever.

The appearance of antibodies against chemical fractions of hemolytic streptococci about the time of onset of rheumatic symptoms (Coburn and Pauli, 1932, Todd, 1932) suggests that hemolytic streptococcus infection has recently occurred and clinical observations support this relation (Sheldon, 1931, Collis, 1931, Coburn and Pauli, 1935). It may be assumed that the presence of streptococcus antibodies (precipitins, antihemolysins, etc.) is the result of hemolytic infection rather than a characteristic of the rheumatic state.

On the one hand, tonsillitis and other infections with hemolytic streptococci often precede acute manifestations of rheumatic fever and appearance of the latter may be coincident with the appearance of specific antibodies, on the other hand, non-hemolytic streptococci have been recovered from patients suffering from the disease. It is true that the peculiar lesion of rheumatic fever, namely, the Aschoff body, has some characters in common with lesions produced by serum sensitization. Nevertheless evidence that sensitization to products of one or many types of streptococci is an essential precursor to the occurrence of rheumatic fever is as yet lacking.

*Glomerulonephritis* Acute glomerular nephritis appearing as a complication of acute infection with hemolytic streptococci usually during convalescence may be referable to sensitization (Schick, 1907, von Pirquet, 1911). In view of the suggestion that the rash of scarlet fever is an allergic reaction, it is noteworthy that the Dick reaction disappears as rapidly in scarlatinal patients who develop acute nephritis as in those that pursue an uncomplicated course. Longcope (1929) has found that patients with acute and subacute nephritis following acute tonsillitis may exhibit exaggerated skin reactions to filtrates of broth cultures of hemolytic streptococci.

Experimental studies on the one hand furnish uncertain evidence of the relation of hypersensitiveness to the production of glomerular nephritis and on the other hand glomerular nephritis seems to have been produced in the absence of allergic phenomena. The experi-

ments of Klinge and Knepper (1935) and of Knepper (1935) in which glomerular nephritis was found in several rabbits that survived thirty intraperitoneal injections in great doses (10 cc) of an emulsion of rabbit's kidney, in each instance accompanied by intravenous injection of 2 cc of pig's serum, have doubtful significance. Experimental production of glomerular lesions has been somewhat more successful with non-hemolytic than with hemolytic streptococci, but the resulting lesions seem to have been focal rather than diffuse.

Focal glomerulonephritis with thrombosis of capillary loops of the glomerular tufts similar to that associated with human bacterial endocarditis caused by *Streptococcus viridans* has been produced experimentally both by single and by repeated introduction of the microorganism into the veins of animals (Kinsella and Sherburn, 1922, in dogs, Clawson, in rabbits, Rich, Bumstead and Frobisher, 1929). By repeated injection of *B. coli*, *Streptococcus viridans* or *Staphylococcus aureus* in immense doses (up to 10 to 20 cc of an emulsion containing the culture from one to three agar tubes) repeated 6 to 19 times at intervals of several days, Masugi and Isibasi (1936) produced in some instances abscesses and in others glomerular nephritis characterized by proliferation of endothelial cells of the glomerular capillaries. It is doubtful if these lesions occur as the result of sensitization or as the result of repeated contact of the capillary endothelium with microorganisms brought by the blood stream in great number. Allergy is evidently not essential to the occurrence of diffuse glomerulonephritis for Masugi (1934) and Fahr (1935) have described the production of diffuse glomerular nephritis resembling the human lesion by a single injection of what they designate as nephrotoxic serum.

The evidence that is available gives little support to the opinion that the diffuse glomerulonephritis that follows infection with hemolytic streptococci is referable to specific sensitization to products of this microorganism but it does not exclude this plausible suggestion.

*Lobar pneumonia* At the beginning of the century Wadsworth (1904) found that virulent pneumococci injected into the trachea of normal rabbits caused fatal bacteremia, in some instances associated with bronchopneumonia, whereas when previously inoculated animals were treated in the same way there was diffuse inflammation of the

lungs, perhaps comparable to lobar pneumonia, and no invasion of the blood stream. Inhibition of bacteremia has been repeatedly confirmed but the production of lobar pneumonia has been questioned. The occurrence of widespread inflammation of the lungs with some of the characters of lobar pneumonia, following the introduction of foreign serum into the trachea of rabbits sensitized to the same protein (Fried, 1933), gives little insight into the pathogenesis of lobar pneumonia. Sharp and Blake (1930) sensitized rabbits to autolysates of pneumococci and found that they produced diffuse inflammation of the lung when injected into the trachea of sensitized animals, whereas in normal animals there was no evident exudate.

In rabbits repeatedly injected intracutaneously with killed pneumococci cutaneous and corneal hypersensitiveness may be demonstrated with nucleo-protein of pneumococcus and with filtrates from which coagulable proteins have been removed (Juhanelle and Rhoads, 1932), but when these animals receive intravenous injections of pneumococci the histological changes in the lungs are not different from those that follow similar injections into normal animals. The lesion produced by Stuppy, Cannon and Falk (1931), when they injected Type I, II and III pneumococci into the bronchi of rabbits that had received repeated injections of the corresponding microorganism below the buccal mucosa or by insufflation, did not have the gross or microscopical characters of lobar pneumonia. It is noteworthy that Opie, Blake, Rivers, Small and Freeman (1921), and Blake and Cecil (1930), have produced typical lobar pneumonia in monkeys by injecting small quantities of pneumococci into the trachea of normal animals, sensitization is evidently not essential to the production of lobar pneumonia in these animals.

Antigen derived from pneumococcus produces no skin reaction during the acute stage of lobar pneumonia but during convalescence a large proportion of patients develop cutaneous hypersensitiveness (Clough, 1915, Herrold and Traut, 1927, etc.). During convalescence from pneumonia the polysaccharide of the pneumococcus produces an immediate skin reaction which runs its course in one or two hours (Tillett and Francis, 1929), whereas pneumococcus protein produces a persistent reaction similar to that of tuberculin. Hypersensitiveness to polysaccharides in rabbits is associated with resistance to the

pneumococcus but hypersensitiveness to the protein is not accompanied by protection

If previously sensitized persons contract lobar pneumonia it must be assumed that desensitization occurs during the acute stage of the disease. Experimental and clinical observations have given no conclusive evidence that sensitization to products of the pneumococcus determines the peculiar characters of lobar pneumonia. They indicate that allergy (sensitization and immunity) may profoundly modify its course.

Allergic inflammation which is the characteristic manifestation of sensitization of tissue is produced by many microorganisms, by products derived from them, by foreign proteins and perhaps by some other substances. Sensitization may be associated with immunity characterized by antibody formation and resistance but there is no necessary parallel between the two. In the complex mixtures of antigens that constitute bacteria, sensitization and immunity may be produced by different antigens, but this relation does not exclude the possibility that in some instances both may be caused by the same agent. The tuberculin type of sensitization differs from that produced by the proteins of foreign sera because it is unassociated with antibodies that serve to transfer it passively by the usual procedure from one animal to another. Nevertheless, in association with the development of local lesions tissues in all parts of the body become more sensitive to the action of the inciting agent and react with allergic inflammation to it.

With allergic inflammation all of the elements that constitute an inflammatory exudate, namely, serum, fibrin, granulocytes, including eosinophilic leucocytes, and histiocytes, accumulate with greater rapidity and in greater number than in the normal animal, antibodies if present in the blood are brought to the site of inflammation in increased quantity. These processes fix both foreign proteins, including doubtless those derived from microorganisms, and microorganisms themselves, at the site of inflammation so that passage from the site of inoculation into the blood stream is prevented. Intensified inflammation at the site of entrance of the injurious agent protects internal organs and in consequence anaphylactic shock is

unlikely to occur under natural conditions. In this process of local fixation it is not possible to estimate the relative importance of antibodies, of phagocytes and of the inflammatory reaction itself. In the sensitized animal both fixation and destruction of bacteria occur locally and in the regional lymph nodes.

There is an inverse relation between the virulence of certain bacteria and their ability to induce allergic inflammation. The two factors are probably dependent upon different antigenic agents.

Experimental studies supported by clinical observations have shown that the course and lesions of certain diseases, notably tuberculosis and infection with streptococci, are profoundly modified by allergic inflammation. The peculiar characters of the adult or reinfection type of pulmonary tuberculosis are referable to allergy induced by a first infection.

The evidence assembled to show that allergy is essential to the production of certain diseases, for example, rheumatic fever, glomerular nephritis and lobar pneumonia, is inconclusive even though it is evident that allergic phenomena modify their course. It would be unwise to attempt the elaboration of postulates defining allergic disease after the model of Koch's postulates concerning the causation of infectious diseases. Nevertheless certain conditions must be fulfilled before the allergic origin of a disease can be established. It must be shown that sensitization precedes the production of the disease by its inciting agent. This inciting agent must be capable of reproducing the disease experimentally in sensitized animals. The inciting agent must be demonstrable in such relation to the human disease that its symptomatology and lesions are explainable. Though much suggestive evidence has been collected, these conditions have not as yet been fulfilled for any infectious disease.

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